Efficacy and safety of estetrol (15 mg)/drospirenone (3 mg) combination in a cyclic regimen for the treatment of primary and secondary dysmenorrhea: a multicenter, placebo-controlled, double-blind, randomized study

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Objective: To evaluate the efficacy and safety of the estetrol (E4) (15 mg)/drospirenone (DRSP) (3 mg) combination in a cyclic regimen in Japanese women with primary and secondary dysmenorrhea.
Design: A 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, followed by a 36-week, open-label, extension study.
Subjects: A total of 162 Japanese women with primary and secondary dysmenorrhea.
Intervention: Participants were randomly allocated to either the E4/DRSP group or the placebo group. In the E4/DRSP group, participants orally received one tablet containing E4 (15 mg) and DRSP (3 mg daily) for 24 days, followed by a placebo tablet for 4 days, constituting one cycle. The placebo group was given one placebo tablet daily for 28 days. After 16 weeks, participants in the placebo group were switched to receive E4/DRSP for 36 weeks.
Main Outcome Measures: Absolute change in the most severe total dysmenorrhea score from baseline to the end of the 16-week double-blinded period.
Results: Estetrol/drospirenone reduced the most severe total dysmenorrhea score by 2.3 points from baseline at week 16. The between-group difference was significant (−1.4, two-sided 95% confidence interval, −1.8 to −1.0), showing superiority to placebo. The responder rate, the proportion of participants who achieved a ≥2.0-point reduction in the most severe total dysmenorrhea score from baseline, was 64.3% in the E4/DRSP group, significantly higher than in the placebo group, 28.4%. In the E4/DRSP group, visual analogue scale scores for pelvic pain and dysmenorrhea symptoms during the menstrual bleeding periods were decreased by 44.2 and 42.3 mm, respectively, from baseline at week 16, significantly more than in the placebo group. Objective gynecological examinations suggested amelioration of pelvic tenderness, uterine mobility, and cul-de sac induration in the E4/DRSP group.

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Estetrol/drospirenone improved the quality of life-related questionnaires (interference with daily activities and sleeping) and global impression scores. Intermenstrual bleeding was the primary treatment-emergent adverse event in the E4/DRSP group, similar to combined oral contraceptives. There were no cases of venous thromboembolism and less impact on hemostasis parameters in the E4/DRSP group.
Conclusion: Estetrol/drospirenone is an effective treatment for dysmenorrhea, offering a safe, new treatment option with potentially reduced thromboembolic risk.
Clinical Trial Registration Number: jRCT2011210023. (Fertil Steril® 2025;123:700–8. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Estetrol, drospirenone, estrogen-progestin combination, dysmenorrhea, symptom alleviation

Dysmenorrhea, characterized by painful menstruation, is a common gynecological condition affecting a significant proportion of reproductive age women (1). It causes lower abdominal and back pain occurring just before and during menstruation, often accompanied by other symptoms such as nausea and headache (2).

Primary dysmenorrhea typically occurs in the absence of underlying pathology, whereas secondary dysmenorrhea results from conditions such as endometriosis (3). The pathophysiology of dysmenorrhea involves complex interactions among hormonal, inflammatory, and neurosensory pathways (4). One of the key mechanisms is the release of prostaglandins, particularly prostaglandin (PG) $F_{2\alpha}$ and PG E_2, during menstruation, leading to increased uterine contractility and ischemia, which manifests as pain (5). Pelvic congestion, hormonal imbalances, and psychosocial factors further exacerbate pain manifestations, thereby contributing to the complex pathophysiology of dysmenorrhea (6).

The impact of dysmenorrhea extends beyond physical discomfort, significantly affecting various aspects of women's lives, including quality of life (QOL) and work productivity (7, 8). A Japanese survey demonstrated that 17.2% of women with dysmenorrhea experienced difficulties with work, study, and daily activities that adversely affect QOL (9).

The management of dysmenorrhea aims to alleviate pain and improve QOL. As the first-line treatment, nonsteroidal anti-inflammatory drugs are used because of their effectiveness in inhibiting PG synthesis and reducing uterine contractions; however, combined oral contraceptives (COCs) are prescribed to promise more reliable clinical efficacy (10).

Combined oral contraceptives are commonly used for contraception and dysmenorrhea treatment because of shared actions in suppressing ovarian function and thinning the endometrium (11). Ethinyl estradiol (EE) is widely used as estrogen in COCs; however, COCs may cause significant safety risks, particularly an increased propensity for venous thromboembolism (VTE), with a 3- to 9-likelihood compared with non-COC users (1- to 5-likelihood) (12).

Estetrol (E4) is a native estrogen synthesized exclusively in the fetal liver, reaching maternal circulation through the placenta (13, 14). It interacts with nuclear and membrane estrogen receptors (ERs), as well as membrane ERα (15). Estetrol acts as an agonist of nuclear ERα and as an antagonist of the ERα-dependent membrane-initiated steroid signaling (16, 17). This unique mode of action classifies E4 as the first native estrogen with selective action in tissues differing from selective ER modulators (18).

Early-stage clinical development suggested that a combination of E4 (15 mg) with drospirenone (DRSP) (3 mg) would efficiently suppress ovulation, as well as manage menstrual cycles (19, 20). Furthermore, it was found that E4/DRSP had minimal impact on not only lipid and glucose metabolism, but also on hemostasis parameters (21, 22). Therefore, E4 (15 mg)/DRSP (3 mg) demonstrated excellent contraceptive efficacy, good bleeding control, and no safety concerns in two different phase III studies (23, 24). It received regulatory approval from the European Union and United States in 2021.

This study consisted of a 16-week, double-blind, treatment phase to confirm clinical efficacy, followed by a 36-week open-label extension phase to clarify long-term efficacy and safety in Japanese women with dysmenorrhea treated with the E4 (15 mg)/DRSP (3 mg) combination.

MATERIALS AND METHODS

Study design

This was a 16-week multicenter, randomized, double-blind, placebo-controlled, parallel-group study, followed by a 36-week, open-label extension study. The objective was to confirm the superiority of E4 (15 mg)/DRSP (3 mg) over placebo after 16 weeks, i.e., four treatment cycles (24-day followed by a 4-day hormone-free interval per cycle) with E4/DRSP, and long-term efficacy and safety for 52 weeks in Japanese women with dysmenorrhea.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice protocols and met all local legal and regulatory requirements. The protocol was reviewed and approved by the institutional review board of each study site, and written, informed consent was obtained from all participants. The registration code is jRCT2011210023.

Participants

Women aged ≥20 years who were diagnosed with primary or secondary dysmenorrhea were enrolled. Another critical eligibility criterion was total dysmenorrhea score ≥3 during the baseline observation period. Other eligibility criteria are described in the Supplemental Materials, available online.

Treatment

Eligible participants were randomly allocated to either the E4/DRSP group or the placebo group at an equivalent ratio balanced by dysmenorrhea classification (primary and secondary) after ≥2 menstrual cycles. Participants took one tablet daily from the first day of menstruation after randomization. Participants in the E4/DRSP group were treated with E4/DRSP in a cyclic regimen for four cycles (16 weeks). The placebo group received oral placebo tablets daily for 28 days per cycle over four cycles. After the 16-week double-blinded phase, all participants received 36-week E4/DRSP treatment in a cyclic regimen in the open-label extension phase. In both groups, participants were allowed to take nonsteroidal anti-inflammatory drugs (loxoprofen and ibuprofen) as rescue medications as appropriate throughout the study. Randomization codes were developed by the Interactive Web Response System using a permuted-block design managed by an office independent of the clinical investigators and other stakeholders to ensure study blindness.

Evaluating endpoints

The dysmenorrhea score, developed by Harada et al. (25), was defined as the total score of "interference with working activity" and "use of analgesics." In the baseline observation and treatment periods, the participants were required to grade the score using an electronic diary (e-diary) device during bleeding episodes daily. The primary endpoint was the changes in the most severe total dysmenorrhea score from baseline to the end of the four treatment cycles. The secondary endpoints included: pelvic pain score during nonmenstrual bleeding episodes; responder rates of those achieving ≥2.0 points reduction of the most severe total dysmenorrhea scores from baseline; intensities of pelvic pain and dysmenorrhea symptoms rated by visual analogue scale (VAS) scores; gynecological examinations, i.e., cul-de-sac induration, pelvic tenderness, and limitation of uterine mobility; interference with daily activity and sleep on a 5-point scale; and 7-point global impression scales rated by investigators (Clinical Global Impression of Improvement) and participants (Patient Global Impression of Improvement). The secondary variables were collected using an e-diary device by all participants, and questioning or examination by investigators at clinical sites.

Treatment-emergent adverse events (TEAEs) were reported as safety endpoints throughout the study, and investigators determined their severity and causality. Participants recorded bleeding events using an e-diary device. Clinical laboratory tests were also conducted including hemostasis parameters.

Statistical analysis

Sample size was determined to identify a group difference of mean changes in the most severe total dysmenorrhea score from baseline of −1.0 with 90% power at α level of 0.05. The primary analysis was performed for the changes in the most severe total dysmenorrhea score from baseline to the fourth treatment cycle using analysis of covariance. This model included group as a fixed effect and the most severe total dysmenorrhea score at baseline as a covariate, adjusting a strata variable, i.e., disease categories (primary and secondary dysmenorrhea). The point estimate of the group difference (E4/DRSP–placebo) was inferred with a two-sided 95% confidence interval (CI). Missing data were imputed by the last observation carried forward method. Multiple imputation methods were also applied as sensitivity analyses. Efficacy analysis was conducted on the full analysis set of participants who received one or more study drugs and whose dysmenorrhea scores at baseline were obtained. The safety analysis included the frequencies of any TEAEs, drug-related TEAEs, and severity and causality using the safety analysis set of participants who consumed at least one study tablet. All descriptive statistics are expressed as mean ± standard deviation values. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). More detailed methods are described in the Supplemental Materials.

RESULTS

Participants

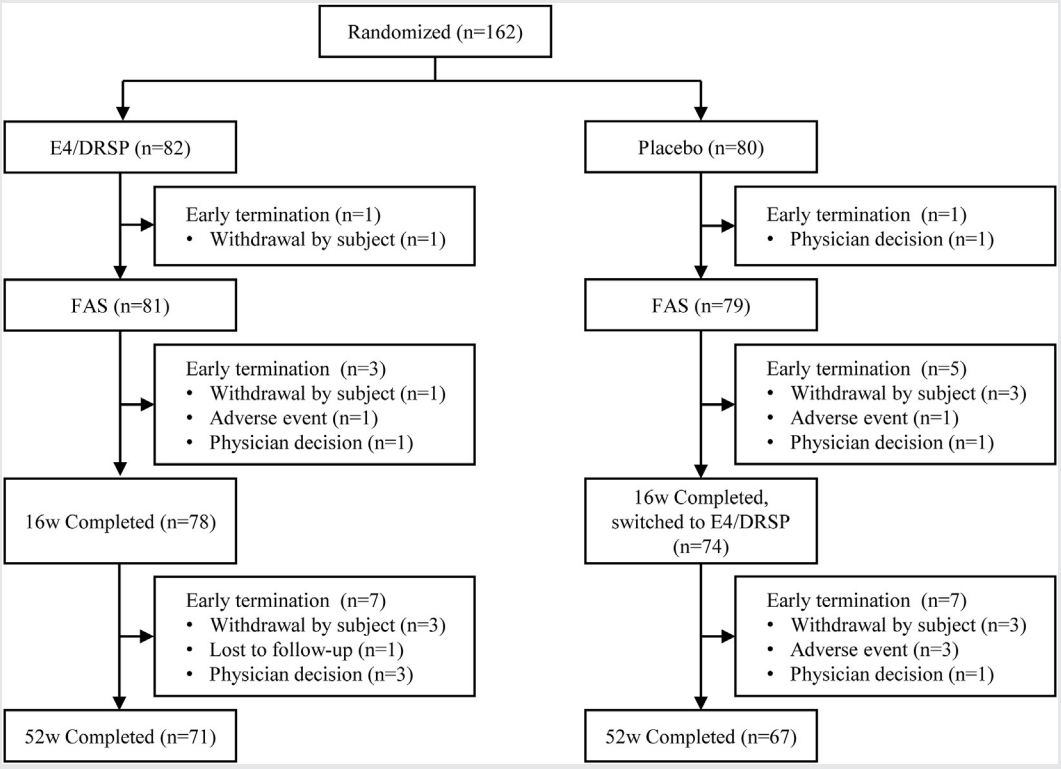
This study was conducted from August 2, 2021, to June 24, 2023, and included 162 participants from 17 clinical sites in Japan. The full analysis set consisted of 81 and 79 participants in the E4/DRSP and placebo groups, respectively, with early termination of eight participants by 16 weeks and 14 additional participants by 52 weeks (Fig. 1). Demographic characteristics were comparable between the groups. The mean age and body mass index were 33.6 years and 21.50 kg/m^2, respectively. Of the 160 participants, 59 (36.9%) and 101 (63.1%) presented with primary and secondary dysmenorrhea, respectively (Supplemental Table 1, available online).

Efficacy

On average, E4/DRSP reduced the most severe total dysmenorrhea score by 2.3 points from baseline after four treatment cycles. As presented in Table 1, the point estimate of the group difference was inferred to be −1.4 (two-sided 95% CI, −1.8 to −1.0; $P<.001$). Multiple imputation methods also provided similar results (Supplemental Table 2). The most severe total dysmenorrhea scores improved steadily during the 36-week open-label extension part in the E4/DRSP group, as well as in the placebo group after switching to E4/DRSP at week 16 (Supplemental Fig. 1, available online). Responder rates were significantly higher in the E4/DRSP group (64.3% [two-sided 95% CI, 51.9%–75.4%]) than in the placebo group (28.4% [two-sided 95% CI, 18.5%–40.1%]) ($P<.05$).

After the four cycles of double-blinded treatment, the pelvic pain VAS score during the menstrual or withdrawal bleeding periods decreased by 44.2 mm from baseline in the

FIGURE 1



Participant flow. Physician decision: the principal investigators determined that there was a breach of the study protocol and decided that premature termination was appropriate due to poor compliance with the study protocol. E4/DRSP = estetrol (15 mg)/drospirenone (3 mg); FAS = full analysis set; 52w = 16-week double-blinded followed by 36-week open-label treatment; 16w = 16-week double-blinded treatment.

Osuga. Efficacy of E4/DRSP on dysmenorrhea. Fertil Steril 2025.

E4/DRSP group; compared with the reduction in the placebo group, and the group difference was −25.6 mm (two-sided 95% CI, −33.7 to −17.4 mm; $P<.001$). Similar results were observed for the symptoms VAS, with an estimated group difference of −25.8 mm (two-sided 95% CI, −33.6 to −18.0 mm; $P<.001$) (Fig. 2A). Marginal changes were similarly observed for pelvic pain and VAS scores during nonmenstrual periods both in the E4/DRSP and placebo groups, with no significant differences after four treatment cycles (Fig. 2A and B).

Stratified analysis of primary and secondary dysmenorrhea suggested less clinically relevant group differences in efficacy for the most severe total dysmenorrhea score, pelvic

TABLE 1

Changes in dysmenorrhea scores from baseline and responder rate after 16-week double-blinded treatment.

	E4/DRSP (n = 81)	Placebo (n = 79)
Baseline, score	4.7 ± 0.89[a]	4.7 ± 0.86
4th cycle (16 wk), score	2.4 ± 1.62	3.8 ± 1.30
Change from baseline to the 4th cycle, score		
Observed	−2.3 ± 1.59 (−2.6 to −1.9)[b]	−0.9 ± 1.26 (−1.1 to −0.6)
Group difference, LSMean[c]	−1.4 (−1.8 to −1.0)	*P*<.001
Responder rate (%)[d]	64.3 (51.9–75.4)[e]	28.4 (18.5–40.1)
		P<.05

Note: E4/DRSP = estetrol (15 mg)/drospirenone (3 mg).
[a] Mean ± standard deviation.
[b] Two-sided 95% confidence interval.
[c] Least square mean.
[d] Proportion of subject who achieved 2 or more reduction of dysmenorrhea scores from baseline.
[e] Two-sided 95% confidence interval with the Clopper-Pearson method.

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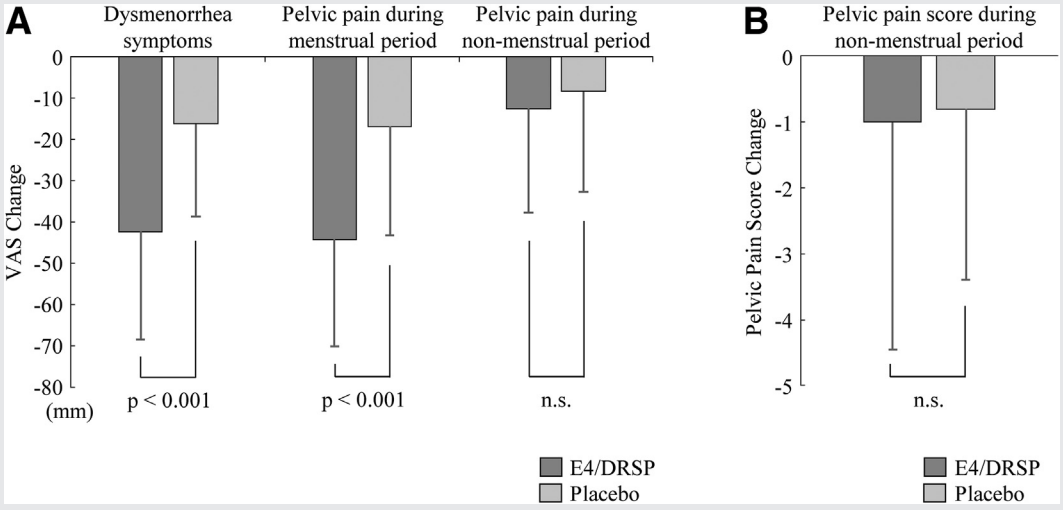
FIGURE 2



Effect E4/DRSP on dysmenorrhea symptoms and pelvic pain. (**A**) Changes in VAS scores from baseline to the end of four treatment cycles. Data are shown as mean/standard deviation values. The two-sample *t* test was used to test for significance. (**B**) Changes in pelvic pain scores from baseline to the end of four treatment cycles. Data are shown as mean/standard deviation values. The two-sample *t* test was used to test for significance. E4/DRSP = estetrol (15 mg)/drospirenone (3 mg); n.s. = not significant; VAS = visual analogue scale.

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pain, and symptoms VAS scores in the E4/DRSP group (Table 2). Rescue medication use was slightly decreased by 1.92 ± 2.86 days in the E4/DRSP group compared with the placebo group (2.61 ± 2.42 days) at week 16 with no significance.

In participants with secondary dysmenorrhea, E4/DRSP was found to ameliorate objective gynecological findings, and the proportion of participants with improvement was 26.9% for pelvic tenderness (placebo: 10.2%), 23.1% for uterine mobility (placebo: 6.1%) and 15.4% for cul-de-sac induration (placebo: 10.2%) after 16-week, double-blinded treatment.

Significant advantages were seen in QOL-related questionnaires and global impression ratings in the E4/DRSP group compared with the placebo group (Supplemental Fig. 2). Furthermore, a close correlation was observed between pelvic pain VAS and the most severe total dysmenorrhea scores, or QOL-related questionnaire grades, with significant parameter estimates in multiple regression formulas ($P<.001$); there was a >1-grade improvement in interference with daily activities and sleeping, along with 2.3-point reduction of the dysmenorrhea score from baseline.

Safety

Treatment-emergent adverse events were reported in 75 of 81 participants (92.6%) and 62 of 79 participants (78.5%) in the E4/DRSP and placebo groups, respectively, over the four treatment cycles (Supplemental Table 3). Intermenstrual bleeding was the most frequently reported TEAE in the E4/DRSP group, and the incidence decreased with treatment cycles. Genital bleeding days were nearly identical across the cycles between primary and secondary dysmenorrhea (Supplemental Fig. 3). Drug-related TEAEs were characterized as those commonly reported for COC products, including nausea (9.9%) and headache (3.7%), and one participant discontinued the study drug because of migraine in the E4/DRSP group. At week 52, the overall profiles of TEAEs were almost similar to those at week 16. In the originally randomized E4/DRSP group, drug-related TEAEs were intermenstrual bleeding (79.0%), nausea (9.9%), and headache (6.2%). No deaths and no VTEs occurred, and little clinically significant modification was reported on D-dimer levels over the course of the 52-week treatment (Supplemental Fig. 4). At week 16, the proportion of participants with D-dimer levels ≥ 1 μg/mL was comparable between the groups (Supplemental Table 4). In all participants, menstruation returned within the 56-day follow-up period.

DISCUSSION

Estetrol/drospirenone demonstrated superior efficacy over placebo for the most severe total dysmenorrhea scores with a significant group difference of −1.4 after 4 cycles (week 16). The responder rate in the E4/DRSP group was 64.3%, highlighting its therapeutic efficacy.

After 16-week, double-blinded treatment, the average pelvic pain VAS score was reduced by 29.9 mm, resulting in approximately 75% of participants having mild pain (5–44 mm), compared with moderate to severe pain at baseline (26). The change from baseline in the pelvic pain VAS score

TABLE 2

Effect of estetrol (15 mg)/drospirenone (3 mg) on dysmenorrhea scores in participants with primary and secondary dysmenorrhea after 16-week double-blinded treatment.

	Primary dysmenorrhea		Secondary dysmenorrhea	
	E4/DRSP (n = 29)	Placebo (n = 30)	E4/DRSP (n = 52)	Placebo (n = 49)
Dysmenorrhea score				
Observed change	−2.4 ± 1.45[a] (−2.9 to −1.8)[b]	−1.2 ± 1.42 (−1.7 to −0.6)	−2.2 ± 1.68 (−2.7 to −1.7)	−0.7 ± 1.13 (−1.0 to −0.3)
Group difference, mean	−1.2 (−2.0 to −0.4)	*P*=.0037	−1.5 (−2.2 to −0.9)	*P*<.0001
Dysmenorrhea symptoms VAS (mm)				
Observed change	−41.9 ± 24.79 (−51.7 to −32.1)	−19.7 ± 27.81 (−30.7 to −8.7)	−42.5 ± 27.40 (−51.0 to −34.1)	−14.4 ± 18.80 (−19.9 to −8.9)
Group difference, mean	−22.2 (−36.6 to −7.8)	*P*=.0031	−28.2 (−38.1 to −18.2)	*P*<.0001
Pelvic pain VAS (mm)				
Observed change	−42.0 ± 23.91 (−51.5 to −32.5)	−19.5 ± 28.34 (−30.7 to −8.3)	−45.6 ± 27.32 (−54.0 to −37.2)	−15.4 ± 25.35 (−22.8 to −8.0)
Group difference, mean	−22.5 (−36.8 to −8.2)	*P*=.0027	−30.2 (−41.2 to −19.2)	*P*<.0001

Note: E4/DRSP = estetrol (15 mg)/drospirenone (3 mg); VAS = visual analogue scale.

[a] Mean ± standard deviation.

[b] Two-sided 95% confidence interval.

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was −44.2 mm, comparable with the pain alleviation reported by a clinical study of a progestin (−45.0 mm) (27).

Closely comparable VAS scores for both pelvic pain and dysmenorrhea symptoms implied that pelvic pain predominates during menstruation. The steadily lower pain intensity during the nonmenstrual period would account for the negligible relief in the dysmenorrhea scores even after E4/DRSP treatment.

In participants with secondary dysmenorrhea, gynecological examinations suggested improvements in the objective findings in the E4/DRSP group compared with the placebo group. The examinations were performed by the same investigators to eliminate inter-rater variability as much as possible.

These desired effects would underlie the improvements in interference with daily activities and sleep, and global impressions after the E4/DRSP treatment, thereby reinforcing the importance of pelvic pain management to ameliorate overall QOL.

On multiple regression analyses, an approximately 2-point reduction in dysmenorrhea scores from baseline improved the interference scores by >1 point, which could be seen as pragmatic verification of the responder definition.

Stratified analysis showed no substantial differences in treatment efficacy on dysmenorrhea and pelvic pain VAS scores between primary and secondary dysmenorrhea. This suggests that the efficacy of the treatment is comparable across both categories, underlining the broad applicability of the intervention.

Safety assessment indicated that intermenstrual bleeding was the primary E4/DRSP-specific TEAE, consistent with phase III results involving 3,417 participants from overseas (28). The events were mild in most of participants, and heavy menstrual bleeding was totally the events of prolonged menstruation. Dysmenorrhea classification had little effect on the number of genital bleeding days during E4/DRSP treatment, differing from a progestin (29), which decreases the burden of interventional management. Other common TEAEs such as nausea and headache were reported as typical for COCs (30).

Combined oral contraceptives are known to increase the risk of VTE, with variations attributed to both estrogenic and progestogenic activities (29, 31). Typical findings in COC users suggest decreased levels of free tissue factor pathway inhibitor and protein S, translating into acquired active protein C resistance, thereby causing increased activities of coagulation factors VIIa and Xa, posing a significant risk factor for VTE (32, 33). The early clinical studies of E4/DRSP showed only a slight elevation in acquired active protein C resistance compared with other COCs such as EE/levonorgestrel and EE/DRSP (34, 35). There were no VTE cases and negligible impact on hemostasis parameters over 52 weeks in this study, implying that E4/DRSP showed relatively lower estrogenicity than other COCs (36).

This study has a limitation in that the menstrual pattern may have indicated to the participant whether active or placebo was given; however, placebo control is widely used to exclude invalid equivalence in noninferiority studies with

active controls because of a primary painful symptom of dysmenorrhea.

CONCLUSION

The results of this study demonstrated that E4/DRSP significantly alleviated dysmenorrhea-associated pain with improvements in objective gynecological examination findings, QOL, and global impressions. Consequently, E4/DRSP was shown to be effective and can thus be recommended as a therapeutic option for dysmenorrhea with potentially reduced thromboembolic risk.

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CRediT Authorship Contribution Statement

Yutaka Osuga: Conceptualization, Methodology, Data curation, Writing – Original Draft. **Takao Kobayashi:** Conceptualization, Methodology, Data curation, Writing – Original Draft. **Akihiro Hirakawa:** Statistical consultation, Writing – Original Draft. **Toshiaki Takayanagi:** Clinical monintering, Investigation. **Masayoshi Nomgai:** Formal Analysis. **Kyaw Tayzer:** Safety monitoring, Writing – Original Draft. **Takayuki Mochiyama:** Medical writing. **Masashi Hirayama:** Conceptualization, Methodology, Data curation. **Jean-MichelFoidart:** Conceptualization, Methodology, Data curation. **Tasuku Harada:** Conceptualization, Methodology, Data curation.

Declaration of Interests

Y.O. reports that medical writing and clinical trial advisory fee payment was made by Fuji Pharma Co., Ltd. based on medical expert contract for the submitted work; clinical trial advisory fee payment from Fuji Pharma Co., Ltd. was made based on medical expert contract; and case study meeting fee payment was made by Fuji Pharma Co., Ltd. based on medical expert contracts, outside the submitted work. T.K. reports that medical writing and clinical trial advisory fee payment was made by Fuji Pharma Co., Ltd. based on medical expert contract for the submitted work. A.H. reports that medical writing and clinical trial advisory fee payment was made by Fuji Pharma Co., Ltd. based on clinical biostatistics expert contract for the submitted work; clinical trial advisory fee payment was made based on clinical biostatistics expert contract; and clinical biostatistics educational seminar fee payment was made based on clinical biostatistics expert contract form Fuji Pharma Co., Ltd., outside the submitted work. T.T. reports that this study was sponsored by Fuji Pharma Co., Ltd.; and all funds for study, salary, and article processing charges are paid by Fuji Pharma Co., Ltd. and Mithra Pharmaceuticals. M.N. reports that this study was sponsored by Fuji Pharma Co., Ltd.; all funds for study, salary, and article processing charges are paid by Fuji Pharma Co., Ltd. and Mithra Pharmaceuticals; and also a patent has been filed with regard to the improvement of cul-de sac induration, pelvic tenderness, and uterine mobility in subjects with endometriosis complicated by adenomyosis. K.T. reports that this study was sponsored by Fuji Pharma Co., Ltd.; all funds for study, salary, and article processing charges are paid by Fuji Pharma Co., Ltd. and Mithra Pharmaceuticals; and also a patent has been filed with regard to the improvement of cul-de sac induration, pelvic tenderness, and uterine mobility in subjects with endometriosis complicated by adenomyosis. T.M. reports that this study was sponsored by Fuji Pharma Co., Ltd.; and all funds for study, salary, and article processing charges are paid by Fuji Pharma Co., Ltd. and Mithra Pharmaceuticals. M.H. reports that this study was sponsored by Fuji Pharma Co., Ltd.; all funds for study, salary, and article processing charges are paid by Fuji Pharma Co., Ltd. and Mithra Pharmaceuticals; and also a patent has been filed with regard to the improvement of cul-de sac induration, pelvic tenderness, and uterine mobility in subjects with endometriosis complicated by adenomyosis. J.-M.F. is a member of the board at Mithra Pharmaceuticals and received financial support for the supervision of this study; and consulting fees from Mithra Pharmaceuticals, outside the submitted work. T.H. reports that medical writing and clinical trial advisory fee payment was made by Fuji Pharma Co., Ltd. based on medical expert contract for the submitted work; clinical trial advisory fee payment from Fuji Pharma Co., Ltd. was made based on medical expert contract; and case study meeting fee payment was made by Fuji Pharma Co., Ltd. based on medical expert contracts, outside the submitted work.

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Eficacia y seguridad de la combinación de estetrol (15 mg)/drospirenona (3 mg) en un régimen cíclico para el tratamiento de dismenorrea primaria y secundaria: un estudio multicéntrico, controlado con placebo, doble ciego, aleatorizado.

Objetivo: Evaluar la eficacia y seguridad de la combinación estetrol (E4) (15 mg)/drospirenona (DRSP) (3 mg) en un régimen cíclico en mujeres japonesas con dismenorrea primaria y secundaria.

Diseño: Estudio de grupos paralelos, multicéntrico, aleatorizado, doble ciego, controlado con placebo, de 16 semanas de duración, seguido de un estudio de extension abierto de 36 semanas de duración.

Sujetos: Un total de 162 mujeres japonesas con dismenorrea primaria y secundaria.

Intervención: Los participantes fueron asignados aleatoriamente al grupo E4/DRSP o al grupo placebo. En el grupo E4/DRSP, los participantes recibieron por vía oral un ciclo de un comprimido al día que contenía E4 (15 mg) y DRSP (3 mg) durante 24 días, seguido de un comprimido de placebo durante 4 días. El grupo de placebo recibió un comprimido de placebo al día durante 28 días. Después de 16 semanas, los participantes del grupo placebo cambiaron y recibieron E4/DRSP durante 36 semanas.

Principales medidas de resultado: cambio absoluto en la puntuación de dismenorrea total más grave desde el inicio hasta el final del period doble ciego de 16 semanas.

Resultados: Estetrol/drospirenona redujo la puntuación de dismenorrea total más grave en 2,3 puntos desde el inicio a la semana 16. La diferencia entre grupos fue significativa (- 1,4, intervalo de confianza bilateral del 95%, - 1,8 a - 1,0), lo que muestra superioridad sobre el placebo. La tasa de respuesta, la proporción de participantes que lograron una reducción de $\geq$2,0 puntos en la puntuación de la dismenorrea total más grave fue del 64.3% en el grupo E4/DRSP, significativamente mayor que en el grupo placebo, 28,4%. En el grupo E4/DRSP, las puntuaciones de la escala visual analógica para el dolor pélvico y los síntomas de dismenorrea durante los períodos de sangrado menstrual disminuyeron significativamente más que en el grupo de placebo en un 44.2 y 42.3 mm, respectivamente, desde el inicio a la semana 16,. Los examenes ginecologicos objetivos sugirieron una mejoría de la sensibilidad pélvica, la movilidad uterina y la induración del fondo de saco en el grupo E4/DRSP. Estetrol/drospirenona mejoró la calidad de vida en los cuestionarios relacionados con la vida (interferencia con las actividades diarias y el sueño) y puntuaciones globales de impresión. El sangrado intermenstrual fue el principal evento adverso surgido del tratamiento en el grupo E4/DRSP, similar a los anticonceptivos orales combinados. No hubo casos de tromboembolismo venoso y menor impacto en los parámetros de hemostasia en el grupo E4/DRSP.

Conclusión: Estetrol/drospirenona es un tratamiento eficaz para la dismenorrea y ofrece una nueva opción de tratamiento segura con potencialmente un reducido riesgo tromboembólico.