ORIGINAL ARTICLE: ENDOMETRIOSIS

Prolonged cyclical and continuous regimens of dydrogesterone are effective for reducing chronic pelvic pain in women with endometriosis: results of the ORCHIDEA study

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Objective: To compare the effectiveness of two different treatment regimens of dydrogesterone in the management of endometriosis-related chronic pelvic pain.
Design: Observational, prospective cohort study over six months.
Setting: Twenty gynecology clinics in the Russian Federation.
Patient(s): Three hundred fifty women from 18 to 45 years of age with endometriosis and chronic pelvic pain with or without dysmenorrhea.
Intervention(s): Dydrogesterone 10 mg 2 or 3 times daily, either between the 5th and 25th days of the menstrual cycle (prolonged cyclical treatment regimen) or continuously (continuous treatment regimen). For all patients, the data cutoff was at six months of treatment.
Main Outcome Measure(s): Intensity of chronic pelvic pain on the 11-point numerical rating scale (after 6 months).
Result(s): A marked reduction in chronic pelvic pain was observed with both the prolonged cyclical and continuous treatment regimens (mean ± standard deviation change from baseline −3.3 ± 2.2 and −3.0 ± 2.2, respectively), with no significant difference between the two groups. With both regimens, patients experienced significant improvements in the intensity of chronic pelvic pain, number of days in which analgesics were required, severity of dysmenorrhea, sexual well-being, and health-related quality-of-life parameters. A favorable safety profile of dydrogesterone was confirmed, and no serious adverse drug reactions were reported during the study.
Conclusion(s): Prolonged cyclical and continuous treatment regimens of dydrogesterone therapy both demonstrated a pronounced and similar reduction in the severity of chronic pelvic pain and dysmenorrhea and led to marked improvements in all study parameters related to quality of life and sexual well-being.

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Endometriosis is a gynecologic disease characterized by chronic pelvic pain, dysmenorrhea (1), infertility associated with reduced ovarian reserve, diminished antral follicle count, and anti-Müllerian hormone levels (2). It has been postulated that endometriosis within the ovary causes impaired oocyte quality (3, 4), thus increasing the possibility of defective implantation. However, when considered in isolation from other infertility factors, endometriosis does not seem to impact pregnancy outcomes in women undergoing in vitro fertilization/intracytoplasmic sperm injection (5, 6). Endometriosis has a considerable negative effect on the health-related quality of life (HR-QoL) and psychological well-being of affected women, with work, private relationships, sexual well-being, and family life often adversely affected (7). The main goal of medical treatment is to minimize the need for surgery, but, ultimately, the treatment of symptoms often requires a combination of medical, surgical, and psychological approaches (8–11). A lifelong, individualized approach, on the basis of patient characteristics and preferences, such as age, presenting symptoms, and fertility status, is common (9, 11–13). However, many women report receiving ineffective treatments for extended periods of time. These treatments are often contraindicated during pregnancy and can have unpleasant side effects (14).

Oral progestogens have different profiles with respect to their potency on the hypothalamic-pituitary-adrenal axis and their effects on breast tissue and genital organs (15). Progestogens can reduce the proliferative activity of the endometrium (16) and induce apoptosis in endometriotic cells, making them effective in the treatment of endometriosis (11). Many treatment regimens include progestogens or combinations of progestogens with other drugs (including estrogens) (11); however, there is a lack of comparative data to inform treatment decisions.

Dydrogesterone is a retroprogesterone with a hydrogen atom at carbon 9 in the β position and a methyl group at carbon 10 in the α position (17). In addition, dydrogesterone contains an additional double bond between carbons 6 and 7, resulting in a "bent" conformation with enhanced rigidity compared with progesterone (18, 19). These structural modifications may account for the high selectivity of dydrogesterone for progesterone receptors and its potent progestogenic activity, with no or negligible agonistic activity at androgen, glucocorticoid, and mineralocorticoid receptors (20). In addition, the higher oral bioavailability of dydrogesterone compared with that of progesterone (21), along with its effectiveness at relatively low doses, may minimize side effects (17).

Dydrogesterone was first reported to be effective for the treatment of endometriosis in the 1960s (15) and is licensed for use in more than 100 countries globally (22). Dydrogesterone can induce atrophy in ectopic endometrial tissue and inhibit the formation of de novo endometriotic tissue while leaving the endometrium unaffected (23), thereby relieving the signs and symptoms of endometriosis (15, 23). Unlike some other therapies, dydrogesterone can be used in women who are pregnant or who are attempting to become pregnant (24).

There are two regimens for the use of dydrogesterone in treating endometriosis: a prolonged cyclical regimen (between the 5th and the 25th days of the menstrual cycle) and a continuous regimen, with doses ranging from 10 to 30 mg daily (25). With many years of market availability, there is clinical experience with dydrogesterone; however, it is unknown whether these regimens are comparable in terms of reducing the severity of endometriosis-related pelvic pain and improving associated HR-QoL parameters. ORCHIDEA was a noninterventional, observational study that aimed to assess whether the observed effects of dydrogesterone treatment in women with endometriosis are related to the choice of treatment regimen, on the basis of real-world data collected in Russia.

MATERIALS AND METHODS

Study Design

This prospective, open-label, multicenter observational study (NCT03690765) compared the effectiveness of two approved regimens of dydrogesterone for the management of endometriosis with chronic pelvic pain. The study was conducted in accordance with national Good Clinical Practice regulations, all applicable national standards, and the Declaration of Helsinki. The study was approved by the Independent Interdisciplinary Ethics Committee on Ethical Review for Clinical Studies (Moscow, Russia) and all local ethics committees. All participants provided written informed consent.

Participants

Patients were recruited in 20 gynecology clinics in the Russian Federation between September 21, 2018, and November 11, 2019. Women (18–45 years of age) with endometriosis and chronic pelvic pain, with or without dysmenorrhea, were eligible if they had all of the following key inclusion criteria: laparoscopy-confirmed endometriosis in the lower abdominal area; a transvaginal pelvic ultrasound for ovarian cyst detection performed not earlier than two months before study inclusion; having been prescribed dydrogesterone according to the recommended dosage schedule for treatment of endometriosis; and no hormonal treatment for two cycles before enrollment. The key exclusion criteria were any concomitant severe disease or genital

disorder or any other condition requiring continuous medical treatment; regular use of analgesics not intended to relieve endometriosis-related chronic pelvic pain; use of hormonal contraception during the previous two menstrual cycles; pregnancy; menopause or premature ovarian insufficiency; contraindications to treatment with dydrogesterone; abnormal findings on cervical cytology test; and treatment for infertility by assisted reproductive technologies.

Data Collection

The patients received dydrogesterone as part of standard clinical/hospital practice as prescribed by the physician. The data were analyzed by subgroup on the basis of the prescribed treatment regimen, with patients receiving dydrogesterone 10 mg 2 or 3 times daily between the 5th and 25th days of the menstrual cycle (prolonged cyclical regimen) or continuously (continuous regimen). The duration of treatment with dydrogesterone was defined by the prescribing physician before inclusion in the program and lasted for up to six cycles or longer. For all patients, data cutoff was at six months of treatment.

The protocol provided for three visits: at baseline (visit 1) and after 3 months (visit 2) and six months (visit 3) of treatment. The primary effectiveness endpoint (assessed in the full analysis set* [FAS*] after propensity score matching) was the comparison of the change in intensity of chronic pelvic pain from baseline to month six between patients receiving the prolonged cyclical regimen and those receiving the continuous regimen of dydrogesterone, measured by an 11-point numerical rating scale (NRS) (as recommended by the Art and Science of Endometriosis meeting) (26), to evaluate symptoms objectively. The secondary endpoints (assessed in the FAS) were changes from baseline to month six in the intensity of chronic pelvic pain (11-point NRS), the number of days per menstrual cycle when analgesics were taken (patient diary data), the severity of dysmenorrhea (11-point NRS), the duration of menstrual cycles, patient-reported sexual well-being (5-point Likert scale), and HR-QoL (Short Form-20 [SF-20]) in the overall population.

An exploratory endpoint was the number of pregnancies in patients with endometriosis in the intention-to-treat (ITT) population and in a subgroup of sexually active patients who did not use contraception at all, including those who were trying to become pregnant. The safety variables included adverse drug reactions (ADRs) and other information relevant to pharmacovigilance.

Statistics

The FAS included all patients who signed the informed consent form, received treatment with dydrogesterone, and had at least one evaluable measurement of the effectiveness parameters. The primary endpoint was assessed in the FAS* population, which included patients from the FAS population who were selected by propensity score matching, which is an effective technique to eliminate the effect of various factors that confound results when comparing groups in observational studies (Supplemental Material, available online) (27). Secondary effectiveness endpoints were assessed in the FAS population, and exploratory endpoints were assessed in the ITT population (all patients who had signed the informed consent form). Safety was assessed in the safety population, which included all patients from the ITT population who received at least one dose of dydrogesterone.

Summary data were obtained using descriptive statistics. Quantitative variables were characterized by mean values with standard deviations (SDs), with qualitative variables characterized by the number and percentage of patients in each category. In addition, 95% two-sided confidence intervals (CIs) were used to evaluate statistical parameters, and the Wilcoxon rank sum test was used to perform intergroup analyses at all time points except baseline, with a P value $\leq$ .05 considered to indicate a significant difference.

Because the primary objective of this study was exploratory, a formal sample size calculation was not performed. However, for the primary endpoint, it was assumed that the SD on the 11-point NRS would be at least 4 (28–30). With a significance level of $P \leq .05$, a power of 0.8, and an expected ratio of 1:1 for patients in the prolonged cyclical and continuous treatment groups, a difference of 1.2 points was expected to be statistically significant (with a total sample size of 350 patients). For a ratio of 1:4 between the treatment groups, the power to show a significant difference of 1.2 points, with a sample size of 350 patients, would be 61%.

For the primary endpoint, all significant factors (covariates) were balanced between the two treatment groups by propensity score matching, and missing data were handled by baseline observation carried forward (31, 32). The analysis of secondary endpoints did not include adjustments for covariates.

RESULTS

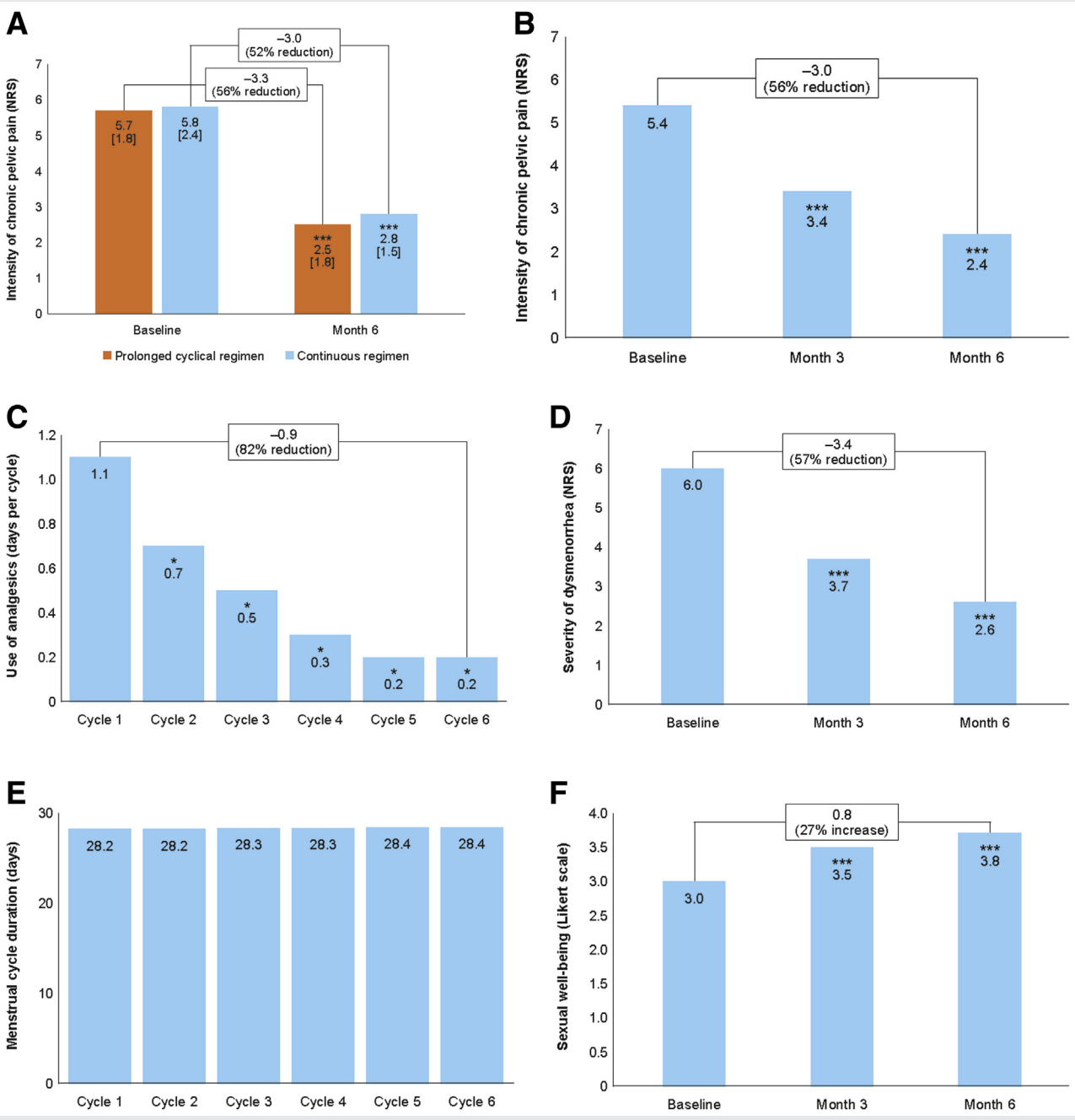
Study Population

A total of 350 patients were screened and included in the ITT population. Of these, 273 patients were assigned to the prolonged cyclical regimen and 77 to the continuous regimen. The FAS population consisted of 350 patients and the FAS* subpopulation consisted of 264 patients (198 receiving the prolonged cyclical regimen and 66 receiving the continuous regimen). A total of 325 patients (92.9%) received up to six months of treatment and completed the study according to the protocol. The reasons for premature withdrawal included loss to follow-up (n = 1, 0.3%), ADR (n = 6, 1.7%), protocol deviations (n = 6, 1.7%), pregnancy (n = 4, 1.1%), withdrawal of consent (n = 5, 1.4%), and other (n = 3, 0.9%).

Baseline Characteristics

The baseline characteristics of the patients are shown in Supplemental Table 1. The mean (SD) age at baseline in the ITT population was 31.1 years (5.0). According to the revised American Fertility Society classification of endometriosis, 65 patients (18.6%) were stage I, 98 patients (28.0%) were stage

FIGURE 1



Summary of effectiveness data. (A) Severity of chronic pelvic pain (FAS*; primary endpoint; mean [SD]). Secondary endpoints (FAS population): (B) severity of chronic pelvic pain (FAS), (C) days per cycle when analgesics needed, (D) severity of dysmenorrhea, (E) duration of menstrual cycle, (F) sexual well-being. FAS = full analysis set; NRS = numerical rating scale; SD = standard deviation. *$P<.05$ vs. cycle 1. ***$P<.0001$ vs. baseline. (A) n = 198 (prolonged cyclical regimen), n = 66 (continuous regimen) at baseline and month 6. (B) n = 350, n = 330, and n = 335 at baseline, month 3, and month 6, respectively. (C) n = 338, n = 330, n = 329, n = 319, n = 319, and n = 325 at cycles 1 to 6, respectively. (D) n = 349, n = 330, and n = 325 at baseline, month 3, and month 6, respectively. (E) n = 336, n = 330, n = 329, n = 319, n = 319, and n = 325 at cycles 1 to 6, respectively. (F) n = 347, n = 325, and n = 323 at baseline, month 3, and month 6, respectively. (E) $P=.839$ between groups (as determined by analysis of variance).

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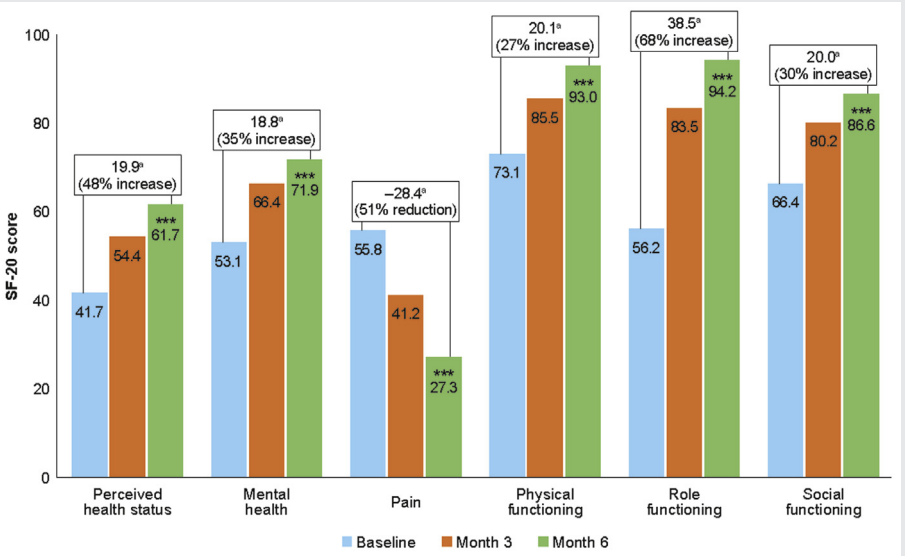
II, 139 patients (39.7%) were stage III, and 48 patients (13.7%) were stage IV. The mean (SD) duration of the menstrual cycle was 28.3 (1.8) days, with 180 patients (51.4%) reporting heavy menstrual bleeding (on the basis of subjective judgment of the volume of blood loss) and 297 patients (84.9%) patients reporting dysmenorrhea.

FIGURE 2



Health-related quality of life according to SF-20 scores (FAS population).
FAS = full analysis set; SF-20 = Short Form-20.
[a]Changes from baseline to month six were calculated using all matched pairs (n = 334), whereas the mean SF-20 scores at each visit include all patients (n = 349, n = 330, and n = 335 at baseline, month 3, and month 6, respectively). ***$P<.0001$ vs. baseline.

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Primary Outcome

After six months of treatment, the mean (SD) change from baseline in the chronic pelvic pain intensity score was –3.3 (±2.2; $P<.0001$ vs. baseline) for patients receiving the prolonged cyclical regimen and –3.0 (±2.2; $P<.0001$ vs. baseline) for patients receiving the continuous regimen (Fig. 1A). A total of 89.9% and 81.8% of patients in the prolonged cyclical and continuous groups, respectively, experienced any reduction in pain intensity. The difference between the two groups was not statistically significant (95% CI –0.763, 0.207; $P = .335$). In the FAS population of patients receiving dydrogesterone 20 mg daily (n = 234), there was a significant decrease in the intensity of chronic pelvic pain (–2.8 ± 2.2 at visit 3; $P<.0001$ vs. baseline). In patients receiving dydrogesterone 30 mg daily (n = 110), the NRS score was –3.5 ± 2.3 at visit 3 vs. baseline ($P<.0001$). In six patients (all in the prolonged cyclical group), the doses were changed (several times in some patients), and therefore they could not be assigned to the 20 or 30 mg daily treatment groups at the next visit(s) (Supplemental Table 2).

Secondary Outcomes

Between baseline and month six, patients receiving dydrogesterone experienced significant decreases in the intensity of chronic pelvic pain (Fig. 1B), the number of days in which analgesics were required (Fig. 1C), and the severity of dysmenorrhea (Fig. 1D); there was no change in the average duration of the menstrual cycle (Fig. 1E). These improvements in signs and symptoms of endometriosis were accompanied by improvements in sexual well-being (Fig. 1F) and in measures of HR-QoL, including perceived health status, mental health, pain, and physical, role, and social functioning (Fig. 2).

There were no significant differences between the two treatment groups in the secondary endpoints (Table 1) except for intensity of chronic pelvic pain and severity of dysmenorrhea. For both of these secondary endpoints, patients receiving continuous treatment experienced a significantly greater reduction in severity scores between baseline and month six compared with those receiving the prolonged cyclical regimen. This observed difference is likely to be because of differences in baseline pelvic pain scores or other interrelated characteristics in the FAS* and FAS analysis populations (Supplemental Table 3).

Exploratory Endpoint

Five women became pregnant during the study: four in the prolonged cyclical treatment group and one in the continuous treatment group. The subgroup of the ITT population consisting of those who were sexually active and not using contraception at baseline included 162 patients: there were four pregnancies (2.5%) in this group.

Safety

During the study, 14 ADRs occurred in 11 patients (3.1%) (2 in the prolonged cyclical treatment group and 9 in the continuous treatment group) (Table 2). All ADRs reported in the study were mild, except for one patient (0.3%) in the

TABLE 1

Secondary endpoints.

Endpoint	Prolonged cyclical regimen n = 273		Continuous regimen n = 77		Total N = 350	
Severity of chronic pelvic pain, 11-point NRS	–2.9 (2.2)[a]		–3.5 (2.2)[a]		–3.0 (2.2)[a]	
Severity of dysmenorrhea, 11-point NRS	–3.3 (2.4)[a]		–4.5 (2.3)[a]		–3.5 (2.4)[a]	
Sexual well-being, 5-point Likert Scale	0.8 (0.9)[a]		0.9 (1.0)[a]		0.8 (1.0)[a]	
Quality of life, SF-20						
Perceived health status	19.5 (18.1)[a]		21.3 (19.2)[a]		19.9 (18.3)[a]	
Mental health	18.8 (16.4)[a]		18.6 (16.1)[a]		18.8 (16.3)[a]	
Pain	–27.2 (23.4)[a]		–33.4 (25.9)[a]		–28.4 (24.0)[a]	
Physical functioning	20.1 (23.7)[a]		19.8 (23.7)[a]		20.1 (23.7)[a]	
Role functioning	36.5 (45.5)[a]		46.3 (51.7)[a]		38.5 (46.9)[a]	
Social functioning	20.0 (22.7)[a]		20.0 (27.2)[a]		20.0 (23.6)[a]	
	Cycle 1	Cycle 6	Cycle 1	Cycle 6	Cycle 1	Cycle 6
Menstrual cycle duration, days	28.2 (2.6)	28.2 (2.1)	28.4 (3.2)	29.3 (3.1)	28.2 (2.7)	28.4 (2.3)
Analgesic use, days per cycle	1.1 (1.7)	0.2 (1.1)[a]	1.0 (1.7)	0.1 (0.2)[a]	1.1 (1.7)	0.2 (1.0)[a]

Note: Values are the mean (SD) change from baseline at month six in severity of chronic pelvic pain, severity of dysmenorrhea, sexual well-being, and quality of life, and mean (SD) menstrual cycle duration and number of days per cycle when analgesics were taken by treatment group (FAS). FAS = full analysis set; NRS = numerical rating scale; SD = standard deviation; SF-20 = Short Form-20.
[a] $P < .0001$ vs. baseline/cycle 1.

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continuous treatment group who was reported as suffering from moderate depression. The most commonly reported ADR was uterine bleeding, which occurred in four patients (1.1%) and was rated as mild in all cases; all four patients were in the continuous treatment group. There were no serious ADRs or deaths because of ADRs during the study.

DISCUSSION

Endometriosis is a chronic disease that is associated with significant pain and morbidity and has a substantial impact on HR-QoL. Best-practice treatment requires a lifelong personalized management plan with the goal of managing symptoms through the optimal use of medical treatment and avoiding repeated surgical procedures (12, 13). Assessing the success of medical treatments for endometriosis and determining which therapies may suit particular patients is difficult because of the lack of randomized controlled trials and the impact of the placebo effect, as observed in previous studies (33, 34). Costs and side effects often dictate the choice of medical treatment (13); therefore, additional insights to guide the individualization of treatment choices can be of value.

TABLE 2

Safety summary.

Patients, n (%)	Prolonged cyclical regimen n = 273	Continuous regimen n = 77	Total N = 350
Summary of ADRs			
ADR	2 (0.7)	9 (11.7)	11 (3.1)
Mild	2 (0.7)	9 (11.7)	11 (3.1)
Moderate	0	1 (1.3)	1 (0.3)
Severe	0	0	0
ADR leading to premature discontinuation	0	6 (7.8)	6 (1.7)
ADR leading to death	0	0	0
Serious ADR	0	0	0
ADR by MedDRA system organ class and preferred term			
General disorders and administration-site conditions	1 (0.4)	1 (1.3)	2 (0.6)
Asthenia	1 (0.4)	1 (1.3)	2 (0.6)
Immune system disorders	0	1 (1.3)	1 (0.3)
Hypersensitivity	0	1 (1.3)	1 (0.3)
Nervous system disorders	1 (0.4)	0	1 (0.3)
Headache	1 (0.4)	0	1 (0.3)
Psychiatric disorders	0	2 (2.6)	2 (0.6)
Apathy	0	1 (1.3)	1 (0.3)
Depression	0	1 (1.3)	1 (0.3)
Irritability	0	1 (1.3)	1 (0.3)
Mood swings	0	1 (1.3)	1 (0.3)
Tearfulness	0	1 (1.3)	1 (0.3)
Reproductive system and breast disorders	0	5 (6.5)	5 (1.4)
Breast pain	0	1 (1.3)	1 (0.3)
Uterine hemorrhage	0	4 (5.2)	4 (1.1)

Note: ADR = adverse drug reaction; MedDRA = Medical Dictionary for Regulatory Activities.

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This observational, open-label, prospective study of treatment outcomes in women with endometriosis confirmed that dydrogesterone is an effective treatment for endometriosis. Both a prolonged cyclical regimen of dydrogesterone 20 or 30 mg daily taken between the 5th and the 25th days of the menstrual cycle and a continuous regimen of dydrogesterone 20 or 30 mg daily were effective and achieved a comparable reduction in chronic pelvic pain. The combined results from the two regimens indicated a greater reduction of chronic pelvic pain in patients taking dydrogesterone 30 mg daily. It is worth noting that the dosing regimen for each patient was not predetermined by the study protocol, and therefore the combination of data from the dosing regimen results should be interpreted with caution. All patients receiving dydrogesterone experienced significant improvements in severity of dysmenorrhea, sexual well-being, and HR-QoL, as well as a reduction in analgesic use. When these secondary endpoints were analyzed by treatment regimen, the continuous regimen was associated with significantly greater reductions in the severity of dysmenorrhea. This possible treatment difference, along with insights from other studies of dydrogesterone, can provide guidance on how treatment may be individualized to suit the clinical needs of women with endometriosis.

Early studies of dydrogesterone [reviewed by Schweppe et al. (15)] demonstrated that dydrogesterone, generally dosed between 10 and 30 mg daily for various numbers of days per cycle over 3–9 months, is an effective treatment for endometriosis, reducing chronic pelvic pain. Across studies, most women experienced a significant reduction in the number and/or severity of symptoms, and these findings were supported by laparoscopic examination in several trials (15, 35–37). In women with dysmenorrhea, cyclical application of dydrogesterone was shown to induce regular menstruation, with reduced blood loss and fewer days of bleeding (15). Most of the studies reviewed by Schweppe et al. (15) were published between 1960 and 2000, and few provide data on a continuous regimen of dydrogesterone. Therefore, the data from this ORCHIDEA study fill an important knowledge gap, providing a comparison of the two approved regimens for dydrogesterone in the context of contemporary standards for observational studies (38).

The results reported here add to real-world experience demonstrating that dydrogesterone is effective and has a favorable safety profile. These results are consistent with clinical experience and reflect that progestogens, along with analgesics and oral contraceptives, are recommended as first-line therapy for endometriosis-related chronic pelvic pain (12, 13, 39). High-quality evidence supports the use of progestogens in this context; however, clinicians are advised to consider the various side-effect profiles, such as irregular bleeding, as well as irreversible effects, such as thrombosis and androgenic effects, when determining which therapy is most appropriate for individual patients (12, 40, 41). Dienogest is a fourth-generation progestogen that received approval for the treatment of endometriosis in the European Union in 2009 and has been demonstrated to offer several important advantages over combined oral contraceptives (42). Although dienogest exerts a pronounced local effect on endometriotic lesions and associated symptom relief, in addition to an antiovulatory and antiproliferative effect, recent real-world evidence studies have highlighted the need to inform women of possible changes in genital bleeding patterns, mood disorders, and weight gain (43, 44).

Although head-to-head comparisons are lacking, dydrogesterone shows clear benefits compared with other progestogen therapies: it does not suppress ovulation until doses over 30 mg daily, is approved for preconceptional care, and offers a prolonged cyclical regimen (19). In contrast, evidence supporting the first-line use of combined oral contraceptives is limited and of low-to-moderate quality (12, 45); further research is necessary to determine the role of combined oral contraceptives in treating pain-associated symptoms of endometriosis (45). Other pharmaceutical treatments recommended as second-line therapies, such as aromatase inhibitors and gonadotropin-releasing hormone agonists, in addition suffer from a lack of evidence or are associated with severe side effects, such as decreased bone mineral density or hypoestrogenic symptoms requiring add-back estrogen therapy (12, 13, 38, 46). The development of novel oral gonadotropin-releasing hormone antagonists may add a valuable asset to the therapeutic arsenal for symptomatic endometriosis (47–50). Further randomized controlled studies are required to assess these agents, but, along with patient preferences, it is likely that cost and effectiveness will still play a critical part in deciding the best options.

Data from the ORCHIDEA study support the use of a prolonged cyclical or continuous dydrogesterone regimen in women for whom the control of irregular uterine bleeding is important. Unlike other oral progestogen therapies, previous studies have shown that oral dydrogesterone can effectively regulate the menstrual cycle (51, 52), and dydrogesterone treatment is additionally suitable for women who wish to become pregnant, since dydrogesterone has no androgenic side effects and does not inhibit ovulation (19, 24). In addition, dydrogesterone has been shown to reduce miscarriage rates in women with threatened or recurrent miscarriage (53–55).

Dydrogesterone was well tolerated during the study, with a safety profile that was generally in line with previous studies in endometriosis (15, 23) and the well-established safety profile (17). Although most of ADRs occurred in the continuous treatment group, the reported ADRs were all mild (except for a single case of moderate depression in the continuous treatment group).

An implicit limitation of observational studies is bias because of the absence of randomization. In addition, the relatively short duration of the study may limit the applicability of the results. It is notewothy, it is noteworthy that, in this study, the choice of regimen lay with the physician because of the lack of treatment guidelines; hence, treatment selection bias was likely. Continuous rather than cyclical regimens are commonly used in patients with severe pelvic pain, as observed in this study (Supplemental Table 3). With the use of propensity score matching to reduce this bias

(balancing confounding factors between treatment groups), the baseline pelvic pain score was more balanced between treatment groups. Therefore, conclusions regarding effectiveness and comparisons were on the basis of the propensity score-matched sample rather than the overall sample.

Genetic diversity in the progesterone receptor can result in variations in progesterone sensitivity and potential progesterone resistance (a subnormal cellular response to the natural effects of progesterone), resulting in a poor therapeutic response to progestogens (56–58); however, the likelihood of patients' varying responses to progesterone was not taken into consideration in this study. Some of these limitations could be addressed by international, randomized, placebo- or active-comparator-controlled trials. Because of the paucity of new evidence comparing different progestogen therapies for the treatment of endometriosis, further studies are warranted. In ORCHIDEA, five women who were sexually active and not using contraception became pregnant; however, the study did not determine whether these women were actively seeking to become pregnant, and compliance was not evaluated because of the observational nature of the study. Conceivably, in addition, there may be value in investigating the effectiveness of the prolonged cyclical and continuous regimens of dydrogesterone in women with endometriosis who are seeking to become pregnant.

In conclusion, the results of this large observational study confirm that prolonged cyclical and continuous regimens of dydrogesterone were similarly effective in their ability to reduce chronic pelvic pain, the requirement for analgesics, and the severity of dysmenorrhea in women with endometriosis. In addition, both regimens were similarly effective in improving HR-QoL and sexual well-being. The favorable safety profile of dydrogesterone and the robust effectiveness data reported by the ORCHIDEA study will support clinicians in their attempts to personalize treatment for women suffering from endometriosis, enabling them to offer more flexible and convenient treatment regimens.

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