Round-the-clock or start-and-stop: Does the regimen matter when dydrogesterone is used to treat chronic pelvic pain due to endometriosis?

Endometriosis, defined by the presence of endometrial glands and stroma outside of the uterine cavity, is a common cause of chronic pelvic pain and dysmenorrhea (1). Surgical management with excision or fulguration of lesions has been demonstrated to significantly reduce pain symptoms (2). However, because endometriosis is hormonally driven, symptoms often recur.

Medical treatment options for women with ongoing or recurring chronic pelvic pain are limited; the vast majority preclude pregnancy and are contraindicated in women trying to conceive (3). An exception to this rule is dydrogesterone, a potent progestogen with high oral bioavailability. Dydrogesterone may be administered cyclically or continuously at doses of 10–30 mg/d. At these doses, dydrogesterone does not typically suppress ovulation and is, therefore, compatible with conception.

There are few existing data on the optimal dosing regimen for dydrogesterone. Previous studies were published in the 1960s through early 2000s and focused primarily on cyclic administration (4). Currently, there are two dosing regimens: a prolonged cyclic regimen in which dydrogesterone is taken from cycle days 5 through 25 and a continuous regimen. The choice of regimen has been historically based on the experience and preference of individual providers, without data to inform the decision.

In this month's issue of *Fertility and Sterility*, Sukhikh et al. (5) present the results of the ORCHIDEA study, a multicenter, observational, open-label, prospective cohort study from the Russian Federation. Women aged 18–45 years with laparoscopy-proven endometriosis and chronic pelvic pain were treated with dydrogesterone 10 mg 2–3 times daily from cycle days 5 through 25 or continuously. The primary outcome was the change in the intensity of chronic pelvic pain from baseline to month 6 as determined by an 11-point numerical rating scale. Propensity score matching was used to minimize the influence of confounders on the primary outcome. The secondary endpoints were evaluated among the entire cohort without propensity score matching; these included the change from baseline to month 6 in the following: intensity of chronic pelvic pain, number of days per cycle in which analgesics were taken, severity of dysmenorrhea, menstrual cycle duration, sexual well-being, and health-related quality of life. A final exploratory endpoint was the number of pregnancies among patients in the intent-to-treat population.

The full analytic cohort included 350 patients, of whom 273 were treated cyclically and 77 were treated continuously. The primary analysis included 264 patients after propensity score matching; of these, 198 received the cyclical regimen, and 66 received the continuous regimen. The mean change in the chronic pelvic pain intensity score from baseline to 6 months was -3.3 ± 2.2 ($P<.0001$) for the cyclical group and -3.0 ± 2.2 ($P<.0001$) for the continuous group. There was no significant difference in the chronic pelvic pain intensity score between the two groups.

Among all patients treated with dydrogesterone, there were significant decreases between baseline and month 6 in the intensity of chronic pain, number of days of analgesics, and dysmenorrhea severity as well as significant improvements in reported sexual well-being and health-related quality of life. The menstrual cycle length was not influenced by dydrogesterone use. When these secondary outcomes were compared between the cyclical and continuous groups, greater reductions in pain score and dysmenorrhea were observed with continuous treatment compared with cyclical treatment. Of note, the continuous group also had a significantly higher baseline chronic pelvic pain score compared with the cyclical group. Finally, among the intent-to-treat population, there were five pregnancies, four of which occurred in women receiving cyclical treatment.

This multicenter, prospective cohort study is a significant contribution to the existing literature on the treatment of pain due to endometriosis. The findings suggest that dydrogesterone may be administered cyclically or continuously for chronic pelvic pain. The regimen may be selected on the basis of the patient's desires and the experience of the individual clinician.

The study also has several limitations. Its clinical utility is limited by the fact that dydrogesterone is not currently available in the United States. The inclusion of only Russian women and the exclusion of pregnant women and women undergoing assisted reproductive technology limit the study's external validity. Additionally, the observational study design predisposes the findings to selection bias. This is evidenced by a higher mean baseline pain intensity score in the continuous group, suggesting that clinicians may be more likely to prescribe a continuous regimen for patients with more severe symptoms. Another significant limitation is the lack of a control group, preventing any definitive conclusions about the overall efficacy of dydrogesterone. This is particularly significant since the study is industry-funded and, therefore, predisposed to publication bias. Finally, because the follow-up period was only 6 months, the study does not provide any data on long-term outcomes.

In summary, this observational study suggests that 6-month improvements in chronic pelvic pain are similar when dydrogesterone is prescribed cyclically or continuously. These findings may be used to counsel women that the choice of dydrogesterone regimen may be based on their own preferences and the recommendations of their providers.

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