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Successful Experience of Cyclic Progesterone Supplementation in Catamenial Epilepsy

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Dear Editor,

More than one-third of females of reproductive age with epilepsy experience cyclic exacerbation of seizures that are associated with periodic changes in the serum progesterone level (antiseizure activity) and the serum estrogen level (proseizure activity) during the menstrual cycle.[1,2] This condition is known as catamenial epilepsy (CE), and is mainly related to progesterone withdrawal during inadequate luteal phase cycles, which can impair GABAergic inhibition.[3,4] It has been proposed that maintaining high progesterone levels during the perimenstrual period would ameliorate seizure exacerbation (Fig. 1A).[5] We describe two patients with CE who received adjuvant therapy with cyclic progesterone supplementation during the luteal phase.

The first patient was a 22-year-old female diagnosed with idiopathic generalized epilepsy who had normal brain MRI findings and occasional generalized high-voltage spike-and-wave discharges on EEG. Her symptoms were controlled with levetiracetam, which maintained the seizure frequency at once or twice a year. Her menstrual cycle had been relatively regular since menarche at the age of 14 years. While at high school she had experienced generalized tonic or brief absence seizures once or twice a month, which responded poorly to treatment with topiramate and clobazam in that order. The patient had experienced nine seizures during the previous year. It was particularly notable that she complained of more frequent seizure attacks 2–3 days after the initiation of her menstrual cycle that continued during the first week of the cycle. She was prescribed medroxyprogesterone acetate (MPA) tablets (10 mg, once daily) from day 14 to day 28 of her cycle, which was associated with the resolution of CE 12 months later; however, the habitual seizure frequency did not change significantly (Fig. 1B). She was generally satisfied with this treatment, because it allayed her fear of seizures and had made her menstrual cycle regular, despite complaints of slight weight gain and mild headache.

The second patient was an 18-year-old female diagnosed with juvenile myoclonic epilepsy. Her brain MRI findings were normal, but EEG revealed occasional generalized bursts of high-voltage spike-and-wave discharges. Her menstrual cycle had been relatively regular since menarche at the age of 11 years. Generalized tonic–clonic seizures were resolved after administering levetiracetam and sodium valproate, but she experienced perimenstrual myoclonus exacerbations from 3 days before to 3 days after the start of her menstrual cycle. She received cyclic progesterone supplementation using the same protocol as applied to the first patient. Follow-up assessments performed after 12 months revealed a decrease in perimenstrual clustered myoclonus (Fig. 1B). She experienced slight mood instability, which was tolerable, and was satisfied with regular menstruation and milder symptoms.

CE treatment has traditionally focused on the intermittent administration of cyclic medications such as acetazolamide, clobazam, and levetiracetam, or an increase of 25–50% in the dose of anticonvulsants that were already being taken on days of higher seizure susceptibility during menstruation.[6] Recent studies have suggested that a favorable response to cyclic pro-

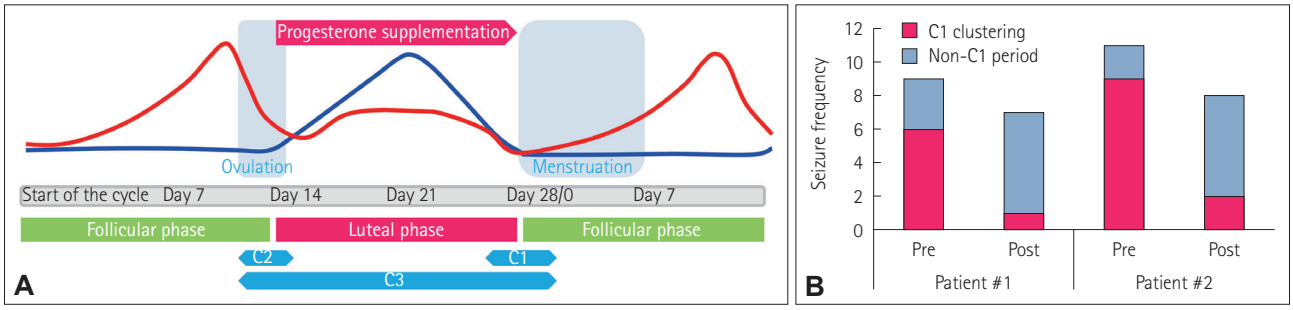

Fig. 1. Treatment cycle and outcome of progesterone supplementation in CE patient. A: Graphs showing hormone fluctuations during menstrual cycles and corresponding catamenial seizure types. There are three patterns of CE: C1 (from 3 days before to 3 days after the start of the menstrual cycle), C2 (day 10 to 13 of the menstrual cycle), and C3 (from 10 days into the menstrual cycle to 3 days into the next menstrual cycle). B: Distribution of numbers of seizure during the 12 months before and after treatment with progesterone supplementation. CE: catamenial epilepsy.

gesterone supplement is due to decreased progesterone levels at the end of the cycle, following the peak in the midluteal phase.[3,4] Although a large-scale phase-3 clinical trial failed to show a significant difference between progesterone and placebo responders, the efficacy of cyclic progesterone supplementation was thought to be greater for progesterone withdrawal, rather than for an estrogen surge or a high luteal-phase estradiol/progesterone ratio.[3] Moreover, progesterone supplements showed a more favorable short-term safety profile compared with anticonvulsants.[6] Subjects in the Herzog trial took natural progesterone 200 mg three times daily, but we administered oral MPA tablets at the standard dose (10 mg, once daily) due to the convenience of taking it according to the advice of the gynecologist.[1] The authors of the Navis trial stated that "synthetic forms of progesterone such as MPA may also play a role in treatment of CE," and reported a 39% decrease in monthly seizures (p=0.02) after treatment with MPA.[6]

The two present cases suggest that progesterone and anticonvulsant combination therapy during the luteal phase of the menstrual cycle is well tolerated and results in a significant reduction in the frequency of seizures associated with CE. Cyclic progesterone supplement therapy should be attempted in females with CE, especially those exhibiting perimenstrual exacerbation.

Author Contributions

Conceptualization: Jon Soo Kim, Seung Hwa Hong. Data curation: Jon Soo Kim. Investigation: Jon Soo Kim, Seung Hwa Hong. Supervision: Won Seop Kim. Writing—original draft: Jon Soo Kim. Writing—review & editing: Jon Soo Kim, Won Seop Kim.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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