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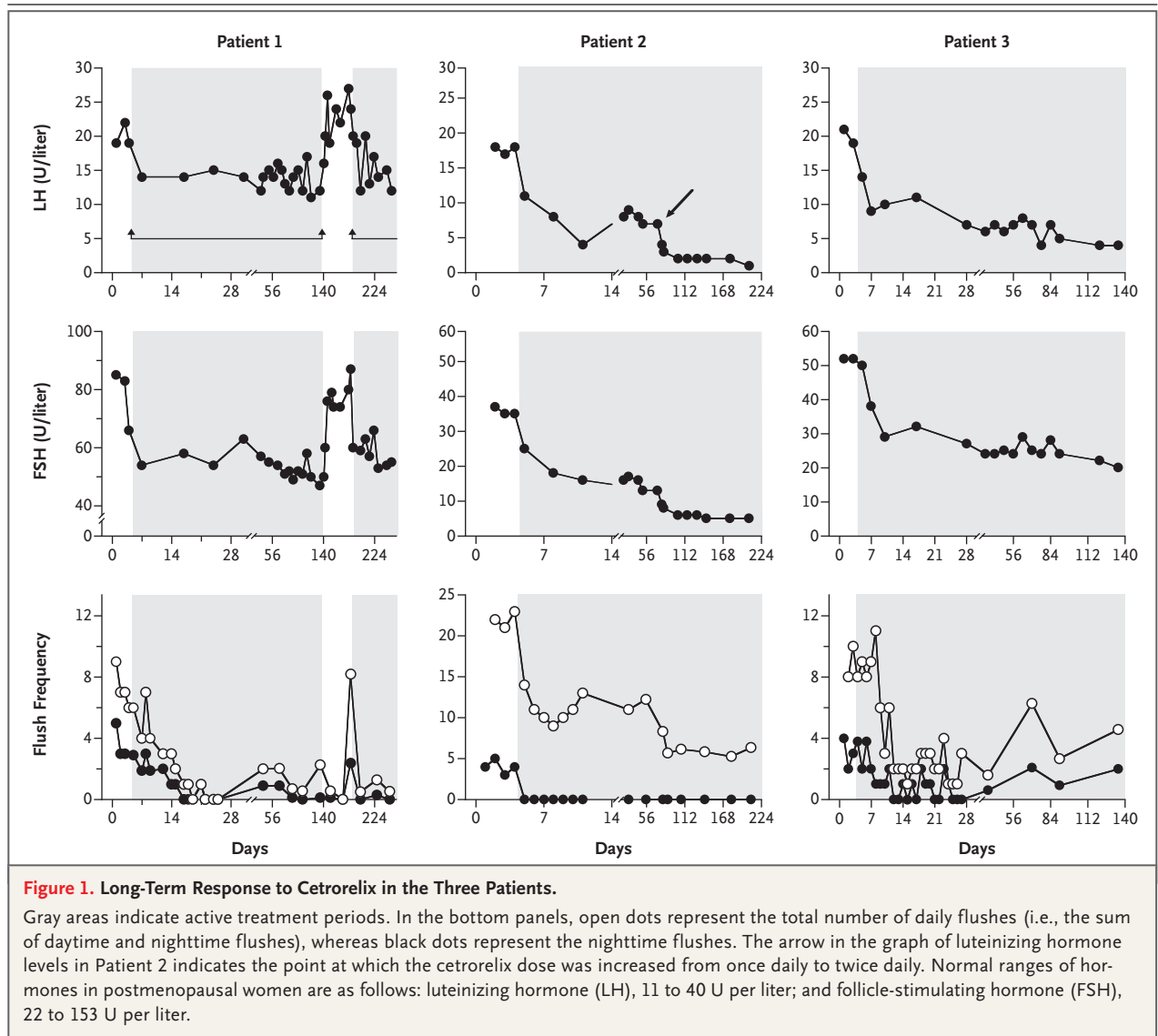
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Luteinizing Hormone–Releasing Hormone and Postmenopausal Flushing

TO THE EDITOR: The trigger for postmenopausal flushing is incompletely understood¹; therefore, it has been difficult to develop new treatments. Neuroendocrine mechanisms, such as increased activity of luteinizing hormone–releasing hormone (LHRH), might be involved.² It has been speculated that a functional link exists through LHRH-producing neurons, which are very close to the hypothalamic thermoregulatory centers.³ To test this hypothesis, we treated three women who had severe postmenopausal flushing with cetrorelix, an LHRH receptor antagonist. Each of the women had undergone menopause as a result of oophorectomy, which had been performed several years previously. Severe flushing developed in Patient 1 (who was 65 years of age) after estrogen-replacement therapy was discontinued. Patient 2 (49 years of age) was a survivor of breast cancer who had been treated with anastrozole. Patient 3 (59 years of age) had undergone successful surgery for stage I endometrial carcinoma.

The short-term response to cetrorelix was studied during a 5-day in-hospital suppression test with a dose of 250 μg given subcutaneously once a day at 9 a.m.⁴ Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were measured on basal samples just before the cetrorelix was administered. Hot flushes were recorded in a diary. The frequency of flushing decreased by 60 to 80% in Patients 1 and 2, but no effect was

observed in Patient 3. Because Patient 3's body-mass index (the weight in kilograms divided by the square of the height in meters) was high (39.8), her dose was increased to 250 μg twice a day; after the increase in dose, the frequency of flushing was reduced by 80% within 5 days. Figure 1 shows the results of long-term outpatient treatment with an initial dose of 250 μg once a day in Patients 1 and 2 and of 250 μg twice a day in Patient 3. Suppression of serum LH and FSH levels and a marked decrease in the frequency of flushing occurred in all three patients, with maximal responses occurring within 4 weeks. The frequency of flushing plateaued at about 12 episodes per day in Patient 2. An increase in the dose to 250 μg twice a day (arrow in Figure 1) further decreased the frequency of flushing to five episodes per day. Patient 3 reported increased flushing after the first month, possibly owing to stressful events in her life. Discontinuation of cetrorelix at week 20 in Patient 1 was associated with an increase in LH levels and FSH levels within 5 days, whereas flushing did not return until about 6 weeks after discontinuation of the drug. The observed efficacy of cetrorelix approaches that observed with estrogen-replacement therapy and markedly exceeds the 25 to 30% decreases observed with placebo.⁵ Despite the limitations of this pilot study (i.e., it was uncontrolled, included few subjects, and did not include objective recordings of flushes), we feel



that responses of this magnitude merit a systematic, placebo-controlled evaluation of LHRH receptor blockade.

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