Melatonin in Health and Disease

To the Editor:

We were pleased about the article by Zimmerman et al.,[1] which confirms our earlier reports about the consistency of the pattern of melatonin secretion throughout the human menstrual cycle[2] and about the temporal relationship between the early morning decline of plasma melatonin levels and the onset of the luteinizing hormone (LH) surge.[3]

To further define the relationship between melatonin secretion and gonadal steroids, we recently studied the pattern of serum melatonin levels during the course of ovarian stimulation in 20 women undergoing in vitro fertilization (unpublished data). Early morning blood samples were obtained every 2 days. Serum melatonin concentrations remained unchanged throughout the cycle independent of the dramatic increase in gonadal hormone levels.

These data indicate that the secretion of melatonin in humans is not modulated by gonadal steroids. At the same time we would like to caution about the conclusion reached by Zimmermann and associates[1] that increased serum melatonin concentrations are unable to prevent or delay the preovulatory LH surge. In the ewe, melatonin alters the frequency of LH pulses, but this action requires some 50 days to become evident[4]; increased plasma levels of melatonin has been reported in women with "hypothalamic" amenorrhea.[2,5] Thus, prolonged elevated serum melatonin levels may be required for the manifestation of altered LH pulses or surge.

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Reply of the Author:

Thank you for your interest in our paper.[1] We recently studied the effect of human menopausal gonadotropin and human chorionic gonadotropin treatment on melatonin secretion in six infertile women. The 24-hour melatonin secretion did not change in this group of women, when the early follicular phase, a state of low estradiol and progesterone concentrations, was compared with the late follicular phase, a state of supraphysiologic estradiol concentration, and to day 6 of the luteal phase, a state of supraphysiologic progesterone concentration.[2] Therefore, the results of our study confirm the observation by Dr. Brzezinski. As stated in the paper,[1] we studied four women who agreed to take 10 mg of melatonin every 4 hours for 7 days starting when the leading follicle measured 15 mm. Under these specific experimental conditions the midcycle luteinizing hormone (LH) was neither delayed nor prevented. We fully agree that under different experimental conditions as indirectly indicated by animal studies[3] and studies in the human,[4] the results might be different. It should be pointed out that melatonin levels are not only elevated in women with hypothalamic amenorrhea,[4] but also in women taking oral contraceptives.[5] Both groups are lacking the midcycle LH surge of spontaneous cycles, which might interfere with chronobiologic systems. Possibly, melatonin as a chronobiologic regulator is elevated in these women to restore cyclicity.

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