This month’s stumper

A double-blind study of fertility-enhancing drugs is conducted. A 28-year-old woman is being treated with sequential doses of a hormone which produces a progressive rise in the hormone’s plasma level over several days. Initially, the patient’s plasma levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) decline, but later FSH and LH suddenly and dramatically increase.

Which of the following hormones is she most likely being treated with?

A. Estrogen.
B. Gonadotropin-releasing hormone.
C. Inhibin.
D. Progesterone.
E. Testosterone.
The correct answer is A.

Kaplan Medical explains why

The drug is promoting changes in estrogen levels and estrogen induced FSH and LH levels that would be expected to be occurring during a normal menstrual cycle. Estrogen levels are relatively low at the beginning of the menstrual cycle but rise slowly during the follicular phase.

Estrogen suppresses FSH and LH secretion during the follicular phase through negative feedback inhibition of the hypothalamic–pituitary–ovarian axis. Once plasma estrogen levels reach a critical threshold (as occurs with the repeated dosing described in this question), and that level is maintained for at least two days, the negative feedback loop changes to a positive feedback loop and a surge in FSH and LH secretion occurs. This sequence occurs at the end of the follicular phase, and the LH surge induces ovulation.

Why the other answers are wrong

Choice B: Gonadotropin-releasing hormone (GnRH) is produced by the hypothalamus and targets gonadotropes in the anterior pituitary. GnRH administration would initially stimulate FSH and LH
secretion, but levels of both hormones would then fall due to downregulation of the GnRH receptors. A pulsatile infusion that mimics the normal pattern of GnRH release from the hypothalamus would promote a sustained increase in LH through GnRH receptor upregulation and gonadotroph sensitization.

**Choice C:** Inhibins are peptide hormones produced by follicular granulosa cells that create a negative feedback control pathway regulating FSH secretion by the anterior pituitary. Inhibins are produced in response to FSH and once released, inhibit FSH secretion. Administration of inhibin would not result in an FSH surge such as that described in the scenario above.

**Choice D:** Prolonged administration of progesterone inhibits GnRH-induced FSH secretion from the anterior pituitary.

**Choice E:** Testosterone normally provides the negative feedback for LH and does not directly affect FSH, although very high nonphysiologic levels of testosterone will reduce plasma FSH due to suppression of GnRH release.

**Tips to remember**

- During the follicular phase, estrogen levels are relatively low but rising.
- Estrogen inhibits FSH and LH secretion during the follicular phase via negative feedback of the hypothalamic–pituitary–ovarian axis.
- Rising estrogen levels sensitize the axis. Once a threshold has been reached, the feedback relationship flips positive, leading to surges in FSH and LH secretion.
- The LH surge induces ovulation.

For more prep questions on USMLE Steps 1, 2 and 3, view other posts in this series.

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