

The Hypothalamic-Pituitary-Gonadal Axis: Puberty, Menstrual Cycle Regulation, and Post-Reproductive Life

F Naftolin (US) [1]

The reproductive life of women is like a symphony, with a conductor and first violinist, and a strict hierarchy of tasks and responsibilities required of each organ. Tight, exquisitely integrated control is required in order that all organs play their parts at precisely the proper moment and with the correct modulation. The leitmotiv menstrual cycle is reiterated until pregnancy or ovarian failure (menopause) intervene. In the event of barren cycles, the re-cycling of the theme is obtained through menstruation and reconstruction of the endometrium. Any dissonance is recognizable as abnormality/disease.

The overall regulation of ovarian and endometrial cycles is the province of the Hypothalamic-Pituitary-Gonadal Axis (HPGA), in which the conductor is the hypothalamus, whose directions are modified by hormonal signals from the ovary. The anterior pituitary gland is the first violin of the orchestra; its response to GnRH is also affected by the ovarian signals. The endometrium, breast, bones, liver, pancreas, brain, immune system tissues and all other organs also receive and respond to the ovarian hormonal signals, maintaining the larger homeostasis of the individual.

As in symphonies, larger rhythms over-arch the reproductive life cycle; childhood is punctuated by puberty that occurs when the neural connections necessary for the hypothalamus to act as a proper transducer of signals from the gonads is complete, the reproductive period begins with a wobbly start and continues until the supply of responsive oogonia is exhausted, and preceded by erratic ovarian cycles, the final act of the failing ovary is reached with the milestone menopause. After that, the gonadotrophins rise but can only drive progestins and androgens from the ovary's steroid secreting tissues.

There are many points of vulnerability in the complex reproductive cycles of girls and women. These are intrinsic (primary), occur pari-passu, or, being downstream of other elements of the reproductive cycle, are secondary (downstream disease). These points of vulnerability will be used to highlight the diagnostic and treatment aspects of reproductive medicine.

Reproduction has evolved with both rewards for success and penalties for failure. Examples of the former include the positive emotions surrounding coitus and child-bearing, while the latter include the energy costs of monthly menstrual bleeding and the acceleration of disease in anovulatory states.

Individual and societal impacts of reproductive failure may not be concordant. This may be best considered in the case of hormonal contraception induced reproductive failure. The stultifying effects of contraception on the workings of Darwinian evolution are contrary to contraception's liberating effects on social evolution. Diagnosis and prevention of the untoward effects of dissonance of the reproductive symphony will be addressed in the remainder of this course.

Naftolin F, Zreik TG, Garcia-Segura LM, Horvath TL. Neuroendocrine control of reproduction, In: DB

Seifer, P Samuels, DA Kniss (Eds): The Physiologic Basis of Gynecology and Obstetrics, Philadelphia, Lippencott, Williams and Wilkins, pp. 63-74, 2001.

Naftolin F, Garcia-Segura LM, Zsarnovszky A, Demir N, Fadiel A, Vondracek-Klepper S, Lewis C, Chang A, Parducz A, Leranth C, Horvath TL. Estrogen-induced synaptic plasticity and pituitary sensitization in the control of the estrogen-induced gonadotrophin surge. *Reprod Sci* 14(2):101-16, 2007.

Morin S, Keefe D, Naftolin F. The separation of sexual activity and reproduction in human social evolution. *Advances in experimental medicine & biology*. 2014;814:159-167.

[1] New York University, NY, USA