The Human Menstrual Cycle

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Abstract

Regular menstrual cycles are the result of predictable cyclic changes in reproductive hormones produced by the pituitary and ovary. A few neurons at the base of the brain in the hypothalamus provide the ongoing stimulus, GnRH pulses, for the synthesis and secretion of LH and FSH which, in turn, stimulate the ovaries to produce the steroids estrogen and progesterone and the small peptides inhibin and activin. It is the feedback relationships between the pituitary and ovarian hormones that provide the basis for the cyclic function of the reproductive system. If fertilization occurs, there is the possibility of a pregnancy which will suppress menstrual cycles for the duration of the pregnancy. Nursing or lactation can also suppress the ovarian cycles, but should not be relied on for birth control. The negative feedback relationship between the ovarian steroids and pituitary gonadotropins is the basis by which hormonal birth control works. Synthetic steroid hormones that can be administered orally suppress the secretion of LH and FSH and thus interrupt the growth and development of ovarian follicles.

Keywords

Hypothalamus • Pituitary • Ovary • LH • FSH • Estradiol • Progesterone • Inhibin • Negative feedback • Pregnancy

4.1 Learning Objectives

After completing this chapter, you should have an understanding of:

- The hormonal changes that occur throughout a menstrual cycle
- Female reproductive hormones and where they are produced

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- How secretion of pituitary and ovarian hormones is regulated
- How birth control pills work

4.2 Introduction

Menstruation is the result of a complex series of hormonal events that causes the growth, demise, and the eventual sloughing off of the uterine lining and discharge through the vagina. Ultimately, the menstrual cycle is a reflection of cyclic changes in secretion of steroid hormones (estrogen and progesterone) from the ovary. The ovarian cycle in women and other female primates is coordinated by a series of chemical signals between the brain, pituitary, and ovary. The most conspicuous sign that occurs as a result of these events is menstruation or the monthly (usually) shedding of blood and cellular debris through the vagina. Monthly menstruation is a sign of regular ovulation, and cycles that are prolonged or not regular suggest that ovarian function is disrupted. Not only does the hypothalamic-pituitary-ovarian (HPO) axis need to function normally for regular cycles, but pathology of other endocrine organs such as the thyroid and adrenal can also result in menstrual cycle disturbances.

The environment within the body (internal milieu) is under tight homeostatic regulation and, in the absence of genetic defects or disease, is kept exceedingly constant. It is this internal homeostatic regulation that allows us to live in a widely fluctuating external environment with relative ease. However, there are environmental factors that can negatively impact reproduction, the foremost of these being availability of food [1]. Reduced energy availability (nutritional stress) is thought to be the main factor in menstrual irregularity [2, 3]. During times when food is limited, physiological functions not necessary for immediate survival, such as growth and reproduction, are put on hold until energy is again readily available. Along with nutritional stress, psychological and physical stress may also influence reproductive cycles. In times of social stress, such as war, there may be menstrual cycle disturbances in 50 % of sexually mature women [4].

4.3 Research Findings

4.3.1 How Is the Brain Involved in Reproduction?

At the transition (puberty) between childhood and adulthood, the initial signal that activates the reproductive system is thought to originate in the brain. It is not clear what event actually initiates the process, but it is the increased secretion of gonadotropin-releasing hormone (GnRH) from a few thousand neurons in the hypothalamus that begins the process of sexual maturation. GnRH is a small peptide (10 amino acids in length) produced in neurons and released from the base of the brain in pulses into a set of specialized vessels, the pituitary portal system, and travels a very short distance to the pituitary gland. These pulses of GnRH occur at about hourly intervals during the first half of the menstrual cycle and cause the release of LH and FSH from the pituitary. We cannot reliably measure GnRH in the peripheral circulation, but there is a very high coincidence of LH pulses in the circulation that follow GnRH pulses in the portal system [5, 6]. Therefore, because LH secretion is a faithful indicator of GnRH release, we can analyze GnRH secretion by measuring LH in the peripheral circulation. Even so, it has been difficult to determine if the amplitude of GnRH secretion changes throughout the cycle, but there is general agreement that the frequency of GnRH release is highest in the follicular phase and slows down in the luteal phase when progesterone is present.

4.3.2 Pituitary Hormones: Luteinizing Hormone and Follicle-Stimulating Hormone

In response to GnRH pulses, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are secreted from the gonadotroph cell in the pituitary. Gonadotroph cells can make either FSH or LH or both. FSH and LH are glycoprotein hormones composed of amino acids and sugars. They are released from the pituitary and travel

through the circulatory system where they bind to specific receptors on the cell surface of specific cells in the ovary in females and the testis in males. The secretion of FSH is regulated by GnRH, estrogen, progesterone, activin, and inhibin. Activin stimulates and inhibin suppresses FSH release. Activin and inhibin are protein hormones secreted by the ovary. Secretion of LH is regulated primarily by GnRH, estrogen, and progesterone. Both FSH and LH can easily be measured in the peripheral circulation, and after puberty, the circulating concentration of these hormones is a useful diagnostic tool for the clinician.

4.3.3 The Ovaries Secrete Steroid Hormone and Release Ova

The ovaries are located in the pelvis, a long distance from the pituitary. LH and FSH are released from the pituitary and travel through the circulatory system, and although almost all cells in the body are exposed to these hormones, they only bind to those cells that have the specific LH and FSH receptors on their surface. How these hormones interact with cells in the ovary is an intricate and fascinating story, but too detailed to describe here. However, the main points regarding the cyclic changes in the ovary are important for understanding the menstrual cycle. At the beginning of the cycle (day 1 of menstruation), FSH is elevated, and this stimulates several follicles (eight to ten) to begin their final stages of growth and development for ovulation. After a few days, one of these follicles becomes the dominant follicle and is destined to be the one that will ovulate or release the mature ovum (egg) into the fallopian tube. As the dominant follicle grows, cells within that structure called granulosa cells release estrogen into the circulation, and estrogen levels increase throughout the first 14 days of the cycle (follicular phase). Estrogen causes growth of the lining of the uterus (endometrium) in preparation for possible implantation of the developing embryo if fertilization occurs. High levels of estrogen are produced when the follicle is ready to ovulate, and this is the signal to the brain and pituitary to release LH to cause ovulation. When the ovum is released from the follicle, the granulosa cells within the follicle transform into luteal cells under the influence of LH. The luteal (yellow) cells primarily make progesterone, the dominant hormone during the luteal phase. Progesterone from the corpus luteum causes additional changes in the uterus in preparation for implantation of the embryo and is a crucial hormone for the maintenance of pregnancy.

4.3.4 The Uterus and Fallopian Tubes

The uterus (womb) is located in the pelvis and is the site of implantation of the fertilized egg after it develops into a blastocyst. The uterus is composed of an outer muscular layer (myometrium) and a lining (endometrium) that undergoes dramatic changes in response to estrogen and progesterone during the menstrual cycle. At the end of the menstrual cycle, the endometrium degenerates and is shed through the vagina as the menstrual flow. As the new cycle begins and the follicle begins to secrete estrogen, the endometrium begins to proliferate and thicken. Hence, the follicular phase of the cycle is also referred to as the proliferative phase. After ovulation, the endometrium becomes secretory in the final preparation for implantation and pregnancy. The luteal phase is sometimes called the secretory phase. If fertilization and implantation do not occur, progesterone and estrogen secretion diminish, and the endometrium degenerates and is shed. A new crop of follicles begins to develop and the cycle begins again.

4.3.5 Feedback Relationships

The hypothalamus, pituitary, and ovary all make and release chemical messengers (reproductive hormones) and communicate with each other with these hormones. The control of the ovarian cycle is complicated, but a few key points regarding the feedback relationships between the pituitary and ovarian hormones are important for understanding how the cycles are maintained.

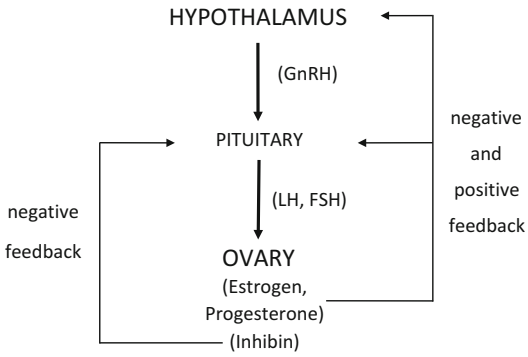

Fig. 4.1 This figure shows the feedback relationships between the ovarian hormones and the hypothalamic-pituitary axis. Steroid (estrogen and progesterone) and protein (inhibin) hormones produced by the ovary regulate the secretion of GnRH from the hypothalamus and LH and FSH from the pituitary to provide the appropriate stimulation for follicular development and ovulation. These feedback relationships are the basis for cyclic ovarian function

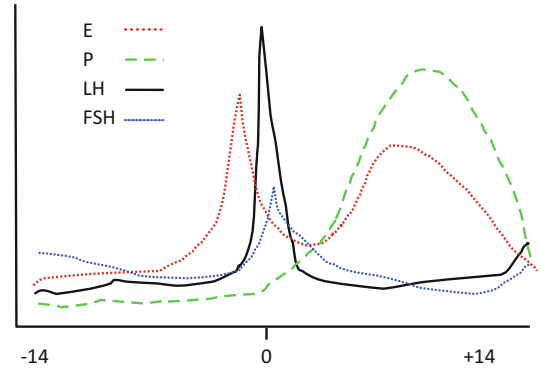

Fig. 4.2 Changing levels of pituitary (LH, FSH) and ovarian hormones (E, P) throughout the menstrual cycle plotted in reference to the day of the ovulatory LH peak. *E* estradiol, *P* progesterone, *LH* luteinizing hormone, and *FSH* follicle-stimulating hormone

As we stated before, at the beginning of the cycle, a few follicles begin to develop under the stimulation of FSH. FSH is elevated at the beginning of the cycle because estrogen, progesterone, and inhibin are low. These hormones from the ovary control FSH secretion, and if the circulating levels of these hormones are low, FSH rises. As the ovarian follicle begins to mature, estrogen and inhibin gradually increase in the circulation and maintain the release of both FSH and LH from the pituitary at a level that will continue the process of follicular maturation. This relationship where LH and FSH are kept in check by the ovarian hormones they stimulate is called negative feedback (Fig. 4.1). Around day 12 of the cycle when the follicle matures and is ready to release the ovum, granulosa cells in the follicle produce levels of estrogen sufficient to trigger the mid-cycle or ovulatory release of LH. This ovulatory surge of LH causes the follicle to rupture and release the ovum. This release of LH triggered by high levels of estrogen is called positive feedback and only occurs at mid-cycle when estrogen levels have exceeded a threshold level for several hours. After ovulation, the corpus luteum (yellow body) makes progesterone, estrogen, and inhibin, and these hormones keep LH and FSH secretion in check. The corpus luteum has about a 2-week lifespan, and unless a pregnancy is established, the corpus luteum will die. At the end of the cycle, estrogen and progesterone fall to low levels, releasing the negative feedback inhibition so that FSH levels in the blood increase and a new group of follicles begin to grow (see Fig. 4.2 for hormonal changes throughout the cycle). These negative and positive feedback signals keep the reproductive hormones in balance and are the basis by which the ovarian cycle is controlled.

4.3.6 Pregnancy and Lactation

When a woman becomes pregnant, menstrual cycles cease because elevated levels of estrogen and progesterone suppress pituitary LH and FSH release and new follicles do not mature. Levels of progesterone and estrogen are initially supported by a hormone from the embryo called human chorionic gonadotropin or hCG. This is the hormone that is measured in pregnancy tests. After a woman delivers and begins to nurse her child, the hormone prolactin is elevated by the suckling stimulus, and this can also suppress follicular development and result in the absence of menstrual cycles. This is called lactational amenorrhea and is a common experience, particularly when the nutritional needs of the child are not supplemented and nursing is the only source of energy. In primitive societies where children

were nursed for several years, lactational amenorrhea served as an effective method of birth control [7]. However, it is not a reliable form of birth control and should not be relied on as such.

Regardless of self-reported sexual activity, pregnancy should always be considered when investigating the cause of amenorrhea in a woman of childbearing age because it is the most common cause of that condition.

4.3.7 Hormonal Birth Control

There are several different birth control methods that use different strategies for controlling fertility. One of these methods, hormonal birth control or oral contraceptives, uses synthetic steroid hormones and the inherent negative feedback system to suppress gonadotropin (LH and FSH) release. These hormonal methods inhibit growth and development of follicles so that ovulation and pregnancy do not occur. Birth control pills contain either a progestin (a compound that acts like progesterone) alone or a combination of an estrogen and a progestin. Progestin-alone pills do not block ovulation but affect the lining of the uterus so that there is a hostile environment for implantation and also retard sperm penetration into the uterus. The steroids in the combination pill suppress LH and FSH release and prevent follicular development and ovulation. The steroid regimen in the combination pill more closely mimics the changes in estrogen and progesterone that occur in the menstrual cycle than does the progestin-alone pill. These combination pills are given so that women who want to have regular menstrual cycles can do so. Modern birth control pills have a very low risk of side effects and are very effective.

4.4 Contemporary Understanding of the Issues

Although our basic understanding of the physiology of the ovarian and menstrual cycle is sufficient for management of many clinical problems, we have a long way to go before we have a complete understanding of the genetic and molecular details of the communication between the brain, pituitary, and ovary that result in regular cycles.

4.5 Future Directions

One of the most pressing health issues of our time is the epidemic of obesity in the western world. Overweight and obese individuals have significantly more health risks than do normal-weight individuals. Overweight individuals have an increased risk for type 2 diabetes, cardiovascular disease, and joint problems. However, even overweight individuals who are physically active are much healthier than those who do not exercise. The dramatic increase in obesity, particularly in young people, has stimulated new research into the physiology of fat. Fat produces many proteins, some of which can impact the reproductive system and alter the function of the metabolic and immune systems as well.

4.6 Concluding Remarks

Regular menstrual cycles are the result of predictable cyclic changes in reproductive hormones produced by the pituitary and ovary. A few neurons at the base of the brain in the hypothalamus provide the ongoing stimulus, GnRH pulses, for the synthesis and secretion of LH and FSH which stimulate the ovary to produce the ovarian steroids estrogen and progesterone and the small peptides inhibin and activin. It is the feedback relationships between the pituitary and ovarian hormones that provide the basis for the cyclic function of the reproductive system. If fertilization occurs, there is the possibility of a pregnancy which will suppress menstrual cycles for the duration of the pregnancy. Nursing or lactation can also suppress the ovarian cycles, but should not be relied on for birth control. The negative feedback relationship between the ovarian steroids and pituitary gonadotropins is the basis by which hormonal birth control works. Synthetic steroid hormones that can be administered orally suppress the secretion of LH and FSH and thus interrupt the growth and development of ovarian follicles.

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