Photo: Miguel Cruz/Dominican Republic

3 THE NORMAL MENSTRUAL CYCLE

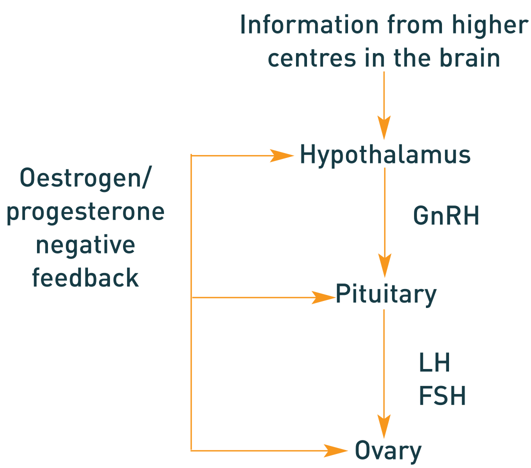
1 Introduction

Basic knowledge of the biology and physiology of the menstrual cycle facilitates understanding of the mechanisms of reproduction and of the action of various methods of contraception. Sexual development and reproductive function are regulated by interaction of the hypothalamus, pituitary gland and ovaries – the hypothalamic-pituitary-ovarian axis.

At the beginning of pubertal development, the sensitivity of the hypothalamic-pituitary-ovarian axis (see Figure 3.1) changes. The hypothalamus starts to release its main peptide, gonadotrophin-releasing hormone (GnRH), in a pulsatile fashion. This, in turn, stimulates the pituitary to release the gonadotrophins follicle stimulating hormone (FSH) and luteinizing hormone (LH). These pituitary gonadotrophins stimulate the ovaries in a cyclical manner, inducing the production of ovarian steroids – androgens, oestrogen and progesterone. The ovarian androgens and oestrogen, together with androgens from the adrenal glands (notably dehydroepiandrosterone), induce the pubertal changes in the female, in particular:

- Breast development;
- Sexual hair growth; *and*
- Maturation of the genital organs, including proliferation of the endometrium.

Figure 3.1 The hypothalamic-pituitary-ovarian axis



Menarche, or the first menstruation, is usually not preceded by an ovulation, but as the hypothalamic-pituitary-ovarian axis develops the ovarian cycle is established. Oestrogen and progesterone have an inhibitory effect on the hypothalamus and the pituitary (negative feedback), homoeostatically regulating the release of gonadotrophins. In the periovulatory phase, increasing oestradiol concentrations stimulate the hypothalamus/pituitary to produce an LH surge, which in turn induces ovum release from the ovary.

Other factors can modulate the cyclical function of the hypothalamic-pituitary-ovarian axis. These influences include:

- Thyroid and adrenal gland activity, as shown by the association of hypothyroidism with menstrual disturbances.
- Olfactory, visual and emotional stimuli, some of which operate via neurotransmitters such as catecholamines, dopamine, serotonin and opioids. The limbic system and the pineal body also influence hypothalamic function, partly through melatonin.
- Nutritional factors, as shown by inhibition of the menstrual cycle in eating disorders or chronic diseases.

2 The ovarian cycle

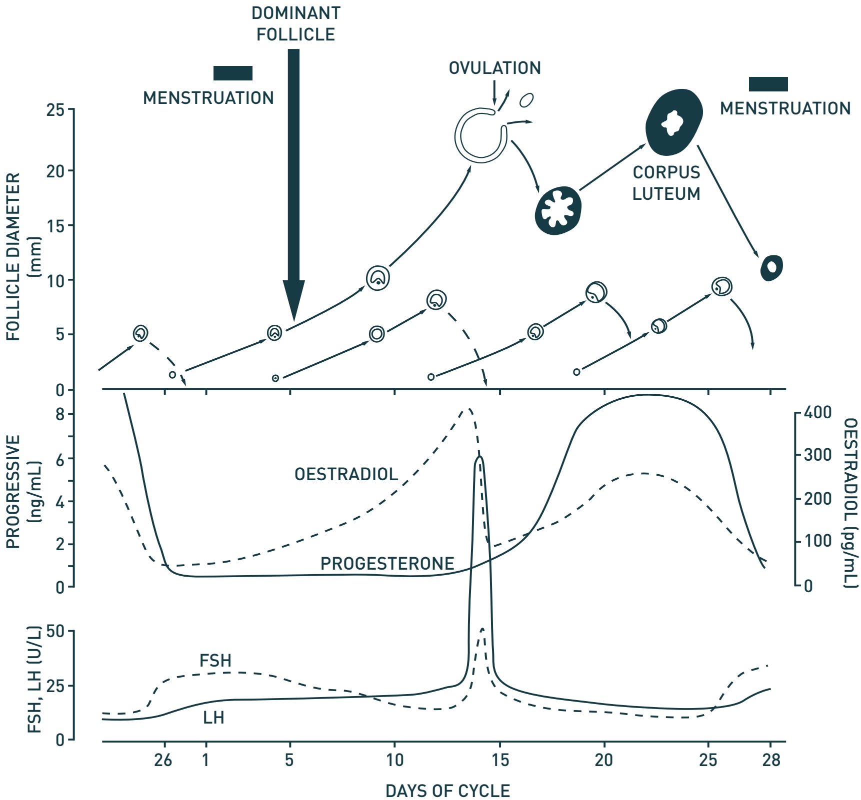
Each fetal ovary contains 6-7 million immature primordial follicles, only a few of which will develop and produce an ovum approximately every month during a woman's fertile life. Most of the follicles are destined to follow a cycle of growth and atresia until the follicle population "expires" at the menopause.

The ovarian cycle (see Figure 3.2) describes the events that occur in the ovary during a menstrual cycle before, during and after ovulation. The ovarian cycle is divided into the follicular phase (pre-ovulatory) and the luteal phase (post-ovulatory).

2.1 The follicular phase

FSH rises shortly before menstruation, stimulating the growth and maturation of a batch of ovarian follicles. The maturing follicles produce oestrogens, mainly oestradiol. By days 5-7 of the cycle one follicle becomes dominant, and the egg (ovum) which will be released from

Figure 3.2 The ovarian cycle



the ovary that month develops within it. The other maturing follicles in the batch recede and become atresic. Small amounts of LH are released continuously throughout the cycle, again in a pulsatile fashion. Some 24-48 hours before ovulation, a surge in oestradiol production by the dominant follicle triggers a surge of LH from the pituitary. This is the final stimulus to ovulation – rupture of the mature graafian follicle and release of the ovum.

FSH and LH can be measured in plasma. Their concentrations are inversely related to ovarian activity, and remain constantly high during the menopause.

2.2 The luteal phase

After ovulation the walls of the ruptured follicle collapse. The cells in the wall accumulate lipids and the pigment carotene, which gives them a yellow appearance. With this transformation the follicle becomes the corpus luteum (yellow body). The corpus luteum produces oestradiol, progesterone and androgens. Progesterone dominates this phase of the cycle and prepares the endometrium to receive the fertilized egg if fertilization occurs. If fertilization does not occur, or if the fertilized egg fails to implant, the corpus luteum regresses 11-14 days after ovulation. Oestradiol and progesterone concentrations in the mid-luteal phase suppress the release of FSH and LH from the pituitary. The atresia of the corpus luteum if no implantation occurs decreases oestrogen and progesterone in the circulation, thereby withdrawing the support of these hormones to the endometrium and leading to menstruation.

3 The endometrial cycle

The ovarian cycle of oestrogen production before ovulation, followed by oestrogen and progesterone in the post-ovulatory phase, is reflected in the endometrium. The endometrium proliferates in both glandular and stromal elements under oestrogen stimulation, in what is called the *proliferative phase*. After ovulation, under the effect of progesterone, the endometrium undergoes secretory changes in the glands and swelling of stromal cells, in what is called the *secretory phase*. As oestrogen and progesterone concentrations fall in the late secretory phase, the endometrial arterioles contract, leading to superficial ischaemia and subsequent shedding of the endometrium. The expulsion from the uterus of this endometrial material, together with blood, is what constitutes the menstrual period. The endometrium starts to repair through the proliferation of basal gland cells within 48 hours.

4 The cervical cycle

In the early pre-ovulatory phase of the menstrual cycle the cervical mucus is thick, sticky and opaque, and forms a plug blocking the cervical canal. With the increasing concentrations of oestrogen as ovulation approaches, the mucus becomes copious, thin, elastic and clear, reaching a peak at ovulation to facilitate the ascent of spermatozoa to the endometrial cavity and upper genital tract. Progesterone reverses these changes after ovulation, producing viscid, scarce, sticky and opaque mucus, which again forms a barrier to spermatozoa. The changes in cervical mucus, accompanied by sensations in the vagina and vulva during the cycle, are the basis of the cervical mucus method of fertility awareness. Together with the physical changes in cervical mucus, there is a pH shift from an acidic pH of around 4 before ovulation to an alkaline pH of 7-8 in the periovulatory and post-ovulatory part of the cycle.

5 Conception

In a fertile cycle, coitus around the time of ovulation will result in rapid entry of sperm through cervical mucus to the upper genital tract. Spermatozoa have been demonstrated in the fallopian tubes 5 minutes after ejaculation (although most sperm take considerably longer), and they can survive in the female genital tract for 5 days or more. Fertilization usually occurs within a few hours of ovulation, in the outer third of the fallopian tube. The fertilized ovum starts to divide in the lumen of the fallopian tube, resulting in a ball of cells called the morula. By day 3 after fertilization the morula (or developing embryo) reaches the uterine cavity. It takes another 2-3 days to start implanting, and approximately another 3 days to implant successfully. On average it takes 6 days after ovulation for the developing embryo to start implantation. Once the embryo is in the uterine cavity, the cells surrounding it start to produce chorionic gonadotrophin, which is detectable in maternal blood from the 8th or 9th day after ovulation. Completion of implantation is regarded as the point of conception. Many fertilized ova (about 50%) do not implant and are lost during the next menstrual flow. Chorionic gonadotrophin maintains the corpus luteum, with continuing secretion of both progesterone and oestrogens until the placenta takes over this function later in the pregnancy.