Department of medicine

Faculty of medicine
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Human Embryology Courses
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OOGENESIS

Introductio*n*

Oogenesis refers to the series of biological events that lead to the formation of cells capable of being fertilized - the ova. It takes place within the female gonad, the ovary, and is completed at the time of fertilization. The gonads (sex glands) in the female are represented by the ovaries and have a dual function:

- **Endocrine:** secretion of female sex hormones (estrogens and progesterone);
- **Exocrine:** the process of oogenesis, that is, the transformation of stem cells called oogonia into female gametes, or secondary oocytes (oocytes II).

The two essential differences in gonadal activity between males and females are as follows:

- *In women, this activity is **limited in time** (from puberty to menopause), whereas in men, it declines gradually but does not cease completely.*
- In women, it is **cyclic**, whereas in men, it is continuous.

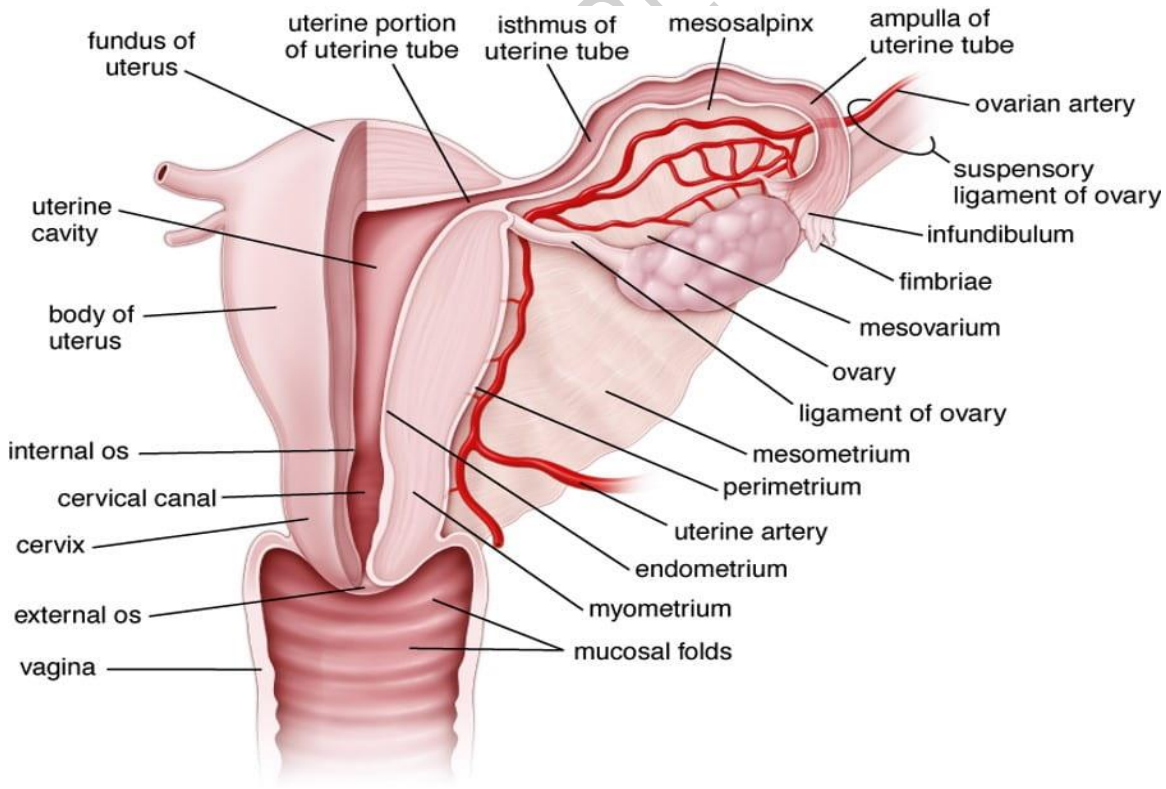

Figure 1: Female reproductive organ.

1. Anatomy of the Female Reproductive System

The female reproductive system consists of two gonads (ovaries) and the genital tract: the Fallopian tubes or oviducts, the uterus, and the vagina (Figure 1)

1.1 Ovaries

The ovaries are located in the pelvic cavity, one on each side. Each ovary measures approximately 1 cm in width and 3 cm in length. It is partially covered by the fimbriae of the oviduct (Fallopian tube).

A histological section of the ovary, from outside to inside, shows:

- the **tunica albuginea**, a connective tissue envelope surrounding the ovary;
- the **germinal epithelium**;
- the **ovarian cortex**, the peripheral part of the ovary, which contains the various stages of folliculogenesis; and
- the **medulla**, which forms the central part of the ovary and is composed of loose connective tissue rich in blood and lymphatic vessels as well as nerves.

1.2. Fallopian Tubes (Oviducts, Uterine Tubes)

They measure 10 to 14 cm in length and connect the ovaries - which they partially cover - to the uterus. The lumen of the Fallopian tubes is lined with an epithelial layer whose morphology varies according to the menstrual cycle.

1.3. Uterus

The uterus has the shape of a pear flattened anteroposteriorly, measuring 6–7 cm in length and about 4 cm in width.

From the outermost to the innermost layers, the uterine wall comprises:

- the **serosa**;
- the **myometrium**, a thick layer of smooth muscle; and
- the **endometrium**, a mucosal layer whose thickness, vascularization, and secretory activity vary throughout the menstrual cycle.

1.4. Cervix (Cervical Canal)

The cervix projects into the upper portion of the vagina. Its vaginal part contains numerous glands that secrete **cervical mucus** and other secretions (vaginal discharge). The cervical mucus selects and facilitates the passage of spermatozoa from the vagina into the uterine cavity.

1.5. Vagina

The vagina is a canal through which copulation and sperm deposition occur. It is sensitive to variations in ovarian hormone levels (*estrogen* and *progesterone*). The vaginal wall consists of a basal lamina connected to dense connective tissue, and a **muscular layer** (muscularis).

1.6. External Genital Organs

The **labia majora** and **labia minora** form two fatty folds covered by epidermis, rich in sweat and sebaceous glands.

The **accessory glands** of the female genital system are:

- the *bulbourethral glands*,
- the *Bartholin's glands*, and
- the *cervical glands*.

2. Folliculogenesis

Folliculogenesis is a cyclic ovarian process occurring within the **ovarian cortex**, consisting of the progressive maturation of the ovarian follicle - a somatic cell structure enclosing an immature oocyte (*primary oocyte*). It begins with the **primordial follicle** and proceeds through several stages, leading either to ovulation or follicular atresia.

2.1. Primordial Follicle

Folliculogenesis starts around the **seventh month of gestation** with the formation of primordial follicles.

A primordial follicle consists of a **primary oocyte (oocyte I)**, arrested in prophase I of meiosis, surrounded by a few flattened **follicular cells**.

At birth, each ovary contains approximately one million primordial follicles. Between birth and puberty, folliculogenesis remains quiescent, leading to degeneration of about 60% of the initial follicular reserve. By puberty, the count decreases to around 400,000 per ovary.

From puberty to menopause, once per month, immediately after menstruation, approximately twenty primordial follicles resume development - typically, only one reaches maturity, while the others degenerate.

2.2. Primary Follicle

At this stage, follicular size increases and is characterized by:

- a large *primary oocyte* arrested in *prophase I*;
- a single layer of **cuboidal follicular cells**;
- the appearance of a **zona pellucida** between the oocyte and the follicular cells;
- an **undifferentiated theca**; and
- a **Slavjanski membrane** separating the theca from the follicular cells.

2.3. Secondary Follicle

The number of follicular cell layers increases, forming the **granulosa**. The theca differentiates into two distinct layers: an **inner cellular theca interna** and an **outer fibrous theca externa**.

2.4. Tertiary (Cavitary) Follicle

The follicle almost reaches its mature size and becomes oval. The large primary oocyte migrates toward a thickened region of the granulosa, forming the **cumulus oophorus**. Within the granulosa, fluid-filled spaces called **antral cavities** appear. The cells of the theca interna acquire the ability to secrete **estrogens**.

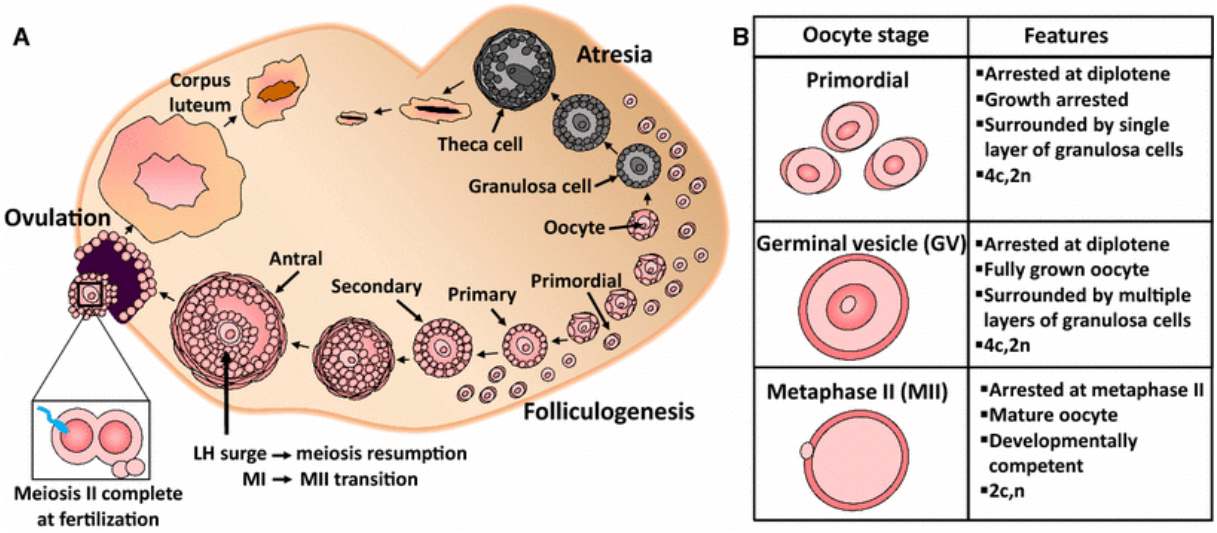

Figure 2: ovarian section: folliculogenesis.

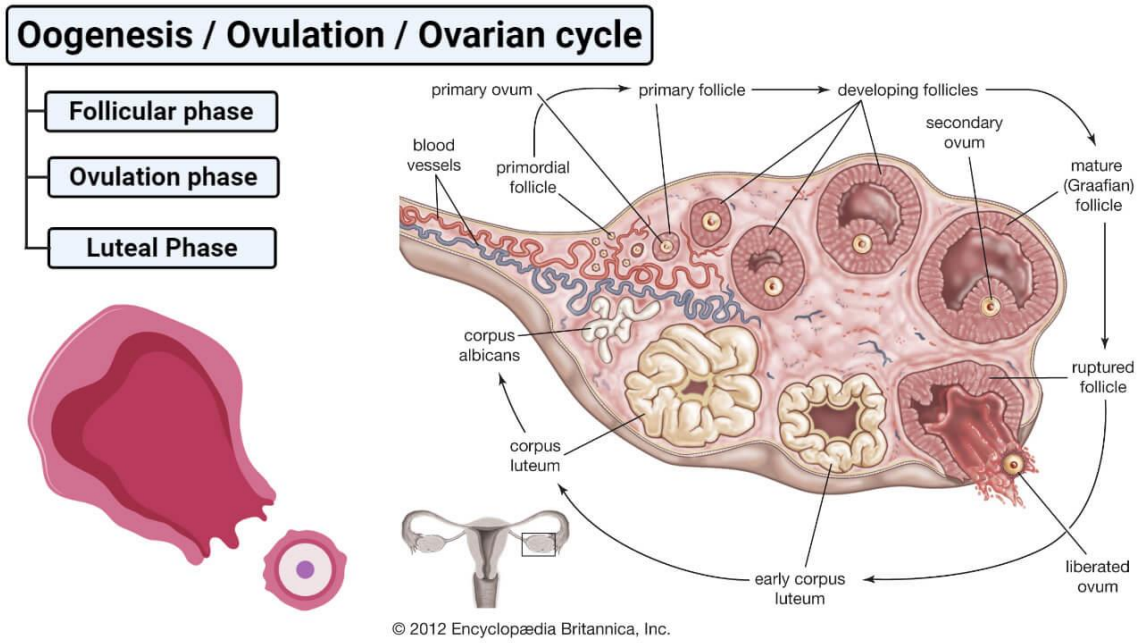

Figure 3: Oogenesis and folliculogenesis.

2.5. Mature (Graafian) Follicle

The follicle reaches its mature size, about 2.5 cm in diameter. The antral cavities fuse to form a single large cavity, the **antrum folliculi**, filled with follicular fluid. The innermost layer of the cumulus oophorus adjacent to the zona pellucida differentiates into the corona radiata.

A few hours before ovulation, the **primary oocyte** completes its first meiotic division, yielding a **secondary oocyte (n chromosomes)** arrested in *metaphase II*, and a **first polar body**, which remains within the zona pellucida.

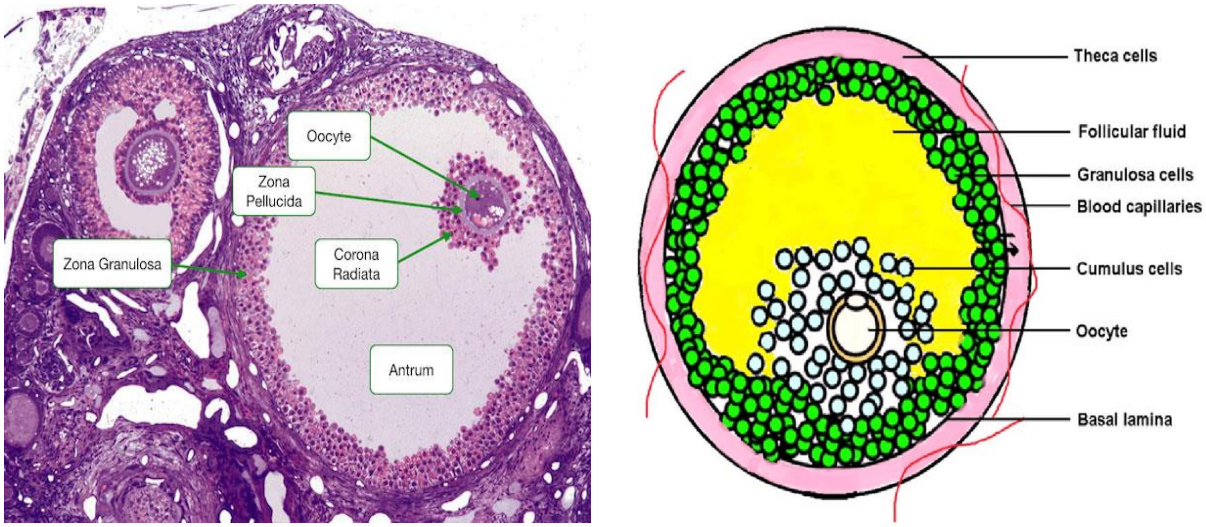

Figure 4: Mature follicle (Graafian follicle).

2.6. Corpus Luteum

After ovulation, the ruptured follicle heals and transforms into a **temporary endocrine gland**, the *corpus luteum*. The granulosa cells become **lutein cells**, capable of secreting **progesterone**, while the theca interna continues to produce **estrogens**.

The corpus luteum can evolve in two different ways:

- **In the absence of fertilization:** it becomes a *menstrual* (*progestational*) *corpus luteum* with a lifespan of about 14 days.
- **In case of fertilization:** it becomes a gestational corpus *luteum*, persisting for about three months before degenerating. The **placenta** then assumes the steroidogenic function.

2.7. Corpus Albicans

Degeneration of the corpus luteum within the ovary gives rise to the **corpus albicans**, which is subsequently phagocytosed by macrophages.

3. Ovulation

Under the influence of a surge in **luteinizing hormone (LH)** and **follicle-stimulating hormone (FSH)** secreted by the anterior pituitary, and the pressure exerted by follicular fluid, the **secondary oocyte**, together with the **zona pellucida, corona radiata**, and part of the **cumulus oophorus**, is expelled from the ovary and enters the outer third of the Fallopian tube (*oviduct*).

Ovulation occurs approximately 36 hours after the LH peak. The **Graafian follicle**, emptied of its contents, collapses and folds, forming the **ruptured follicle**, which subsequently becomes the corpus luteum. The **Slavjanski membrane** disappears, allowing the ingrowth of thecal capillaries into the granulosa, transforming the follicular cells into luteinized cells that secrete lutein pigment, responsible for the yellowish color of the corpus luteum. This process is known as **luteinization**.

3.1. Factors Influencing Ovulation

- **Obesity:** Excess body weight plays a significant role in the regulation of ovulation; hormonal imbalances are frequently observed in such cases.
- **Low body weight or eating disorders:** Similar disturbances occur in women who are underweight or who have experienced anorexia or bulimia.
- **Psychological stress:** Emotional shock, stress, or anxiety can induce temporary anovulation, as the hypothalamic–pituitary axis is under central nervous control.
- **Intense physical activity:** Vigorous or competitive exercise may delay ovulation.

Ovulatory disorders may appear during adolescence or later in life. Generally, such dysfunctions are reversible, and regular cycles may resume, for instance, after pregnancy.

Lifestyle measures are essential: cessation of smoking, balanced diet, and stress reduction are necessary to restore optimal ovulatory function.

Ionizing radiation (X-rays — diagnostic or therapeutic personnel, uranium mines, nuclear plants) and **non-ionizing radiation** (ultraviolet rays, radiofrequencies from communication workers, and electromagnetic fields from cathode-ray screens) can also impair ovulation.

Treatment options to restore ovulation depend on the underlying cause; pharmacologic **ovulation induction** is often sufficient to re-establish normal cyclic function.

4. Menstrual and Uterine Cycles

The menstrual cycle encompasses the physiological phenomena preparing the female body for possible fertilization, occurring periodically in most women.

When fertilization does not occur, the **corpus luteum** (progestational) regresses 10-12 days later, leading to a sharp decline in **progesterone** and **estrogen** levels. The uterine mucosa (endometrium) then detaches, resulting in **menstruation**.

Although the average cycle duration is **28 days**, this is only a conventional reference; actual durations vary considerably among women.

The uterus - the organ where the fetus develops - consists of a muscular wall (*myometrium*) lined internally by the *endometrium*, a mucosa containing glands and blood vessels. The cyclical renewal and desquamation of this mucosa produce the menstrual bleeding.

The uterine cycle involves cyclic modifications of the endometrium over about 28 days, alternating between destruction and reconstruction:

- **Days 0 - 4:** Menstrual phase - the endometrium is shed, leaving a thin residual layer.
- **Days 4 - 14:** Proliferative phase - regeneration and thickening of the endometrium; elongation of tubular glands and vascular growth.

- **Days 14 - 28:** Secretory phase - formation of a “uterine lace” pattern; spiral arteries develop, glands become tortuous, and glycogen secretion increases to nourish the embryo.

The endometrium reaches maximal thickness and prepares for possible implantation.

The first day of menstruation marks the **beginning of a new cycle**.

Note: The uterus measures 6-10 cm in length, 2-4 cm in thickness, and about 5 cm in width, with marked distension during pregnancy.

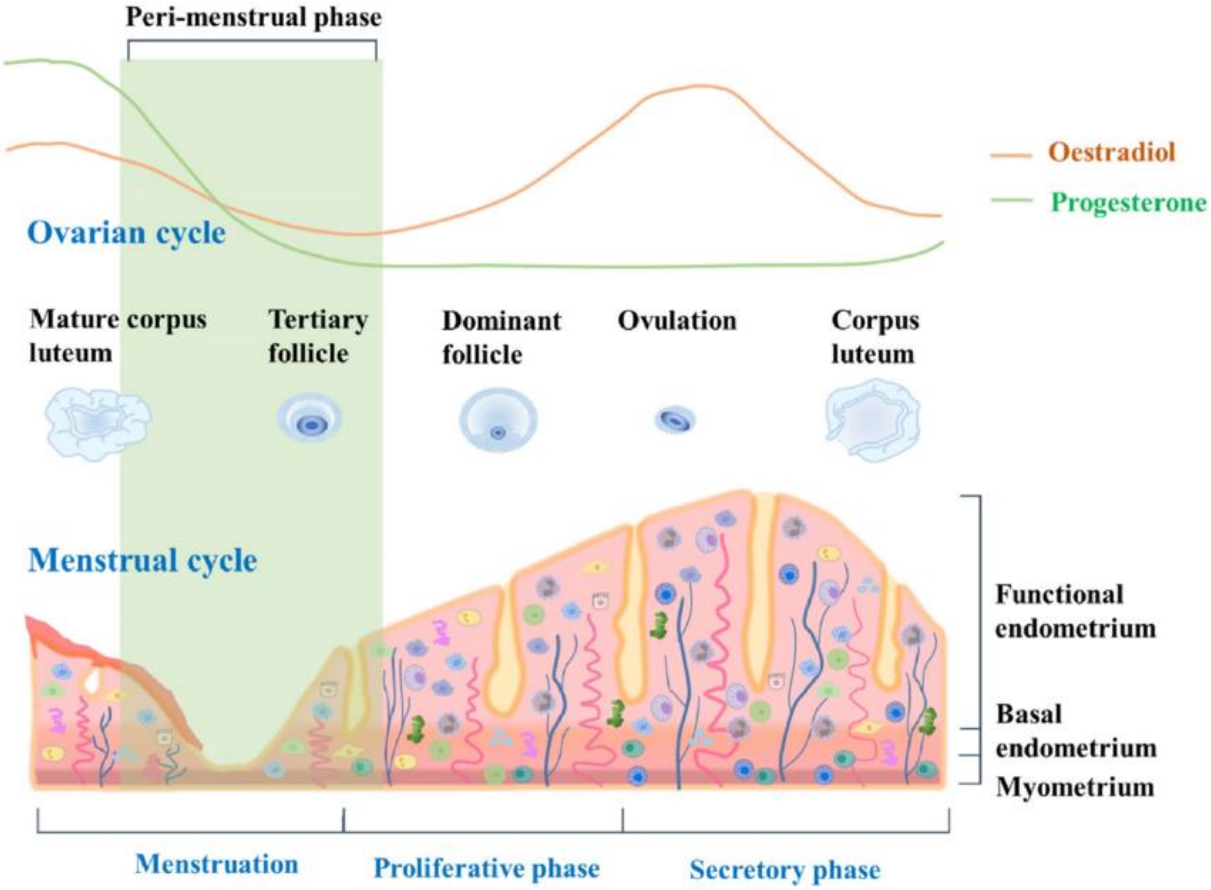

Figure 5: diagram of the changes in the uterine lining during the menstrual cycle

5. Stages of Oogenesis

Oogenesis comprises three phases: a **multiplication phase**, a **growth phase**, and a **maturation phase**.

Phase of Multiplication

This phase involves the **oogonia**, diploid stem cells, and is characterized by successive **mitotic divisions** leading to the formation of **primary oocytes (oocytes I)**, which are also diploid. It occurs during **embryonic and fetal life**

Oogonia:

- are located in the cortical zone of the embryonic ovary;
- are small, spherical cells;
- mostly degenerate around the seventh month of intrauterine life;

- give rise to **primary oocytes (2n chromosomes, 2q DNA)**, which immediately:
  - ✓ become surrounded by follicular cells and a peripheral membrane separating them from the ovarian stroma, forming the **primordial follicle**;
  - ✓ double their DNA content (4q DNA) and enter the first meiotic division, which is arrested in **prophase I**.

At birth, a nonrenewable stock of about one million **primary oocytes** is present, each enclosed within a primordial follicle.

Phase of Growth

This phase is characterized by a marked increase in the size of the primary oocyte. It continues until follicular maturation and involves intense synthesis of **RNA** and **proteins**, essential for fertilization and early embryonic development.

Between birth and puberty, numerous primordial follicles and their oocytes degenerate; approximately 400,000 remain at puberty, but fewer than 500 will reach ovulation during the woman's reproductive life.

Primary oocytes do not complete the first meiotic division before puberty due to a **meiosis-inhibiting factor** secreted by follicular cells.

Phase of Maturation

Each month, between puberty and menopause, at the time of ovulation, the **primary oocyte (2n chromosomes, 4q DNA)** completes its first meiotic division, producing a **secondary oocyte (n chromosomes, 2q DNA)** and a **first polar body (n chromosomes, 2q DNA).** The division is highly unequal, with the secondary oocyte retaining most of the cytoplasm.

Immediately, the second meiotic division begins but arrests again at **metaphase II**, pending fertilization:

- In the absence of fertilization, the oocyte remains at this stage and degenerates rapidly.
- If fertilization occurs, the oocyte completes meiosis, forming a **mature ovum (ovotide)** and a **second polar body**.

Thus, oocyte maturation is more complex than spermatogenesis and presents three specific features:

- meiosis is incomplete, unequal, and prolonged;
- cytoplasmic maturation is synchronous with nuclear maturation;
- the process is closely associated with folliculogenesis.

Fertilization by a spermatozoon activates the **secondary oocyte**, allowing completion of meiosis and formation of the **ovum** and the **second polar body**. In the absence of fertilization, the unfertilized oocyte is expelled, still arrested in metaphase II, at the end of the cycle (10-12 days after ovulation).

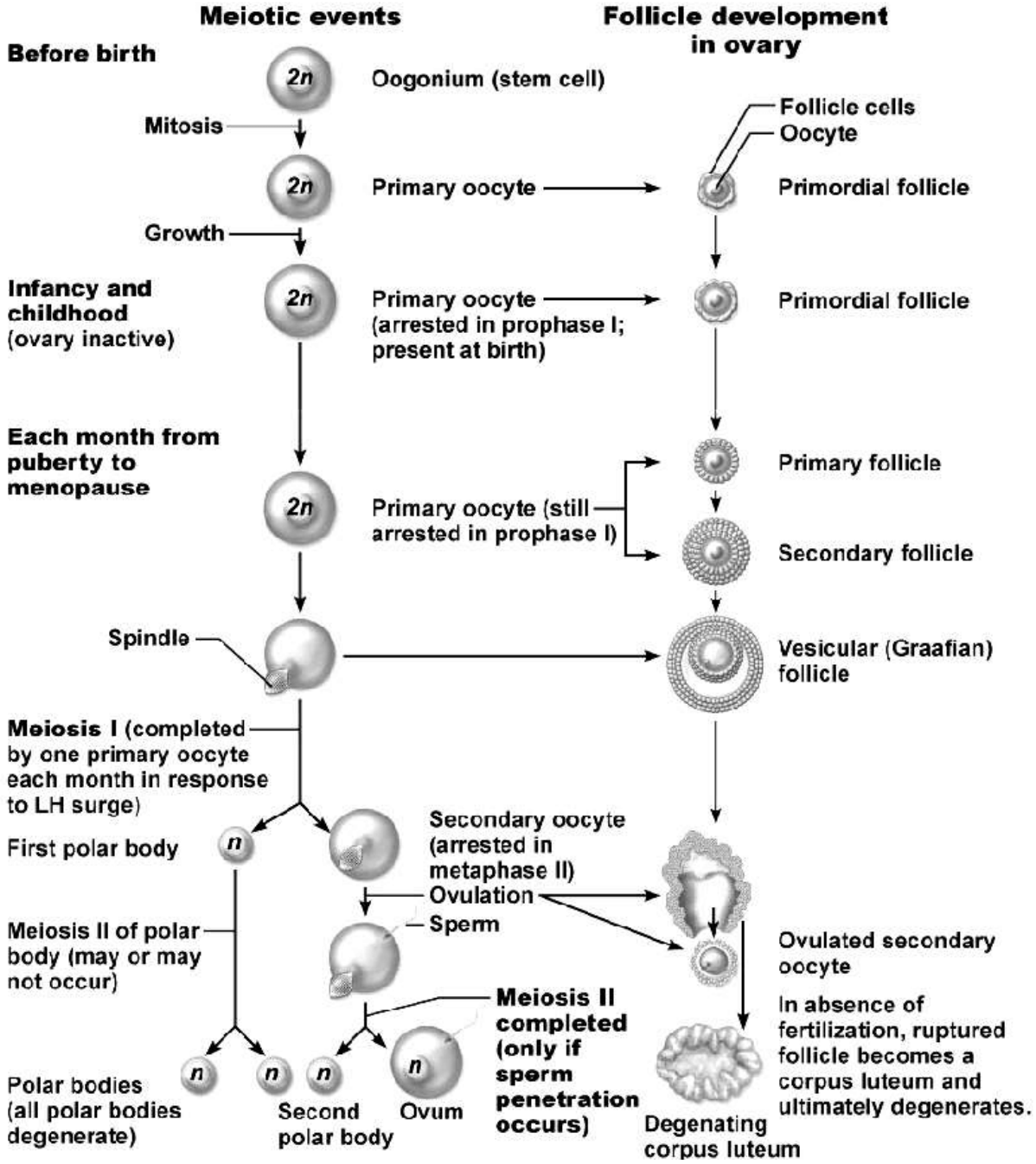

Figure 6: detailed diagram of the stages of oogenesis.

6. Hypothalamic–Pituitary Control

Ovarian activity depends on pituitary regulation through secretion of FSH and LH.

- **FSH (Follicle-Stimulating Hormone): increases during the follicular (preovulatory) phase and peaks simultaneously with LH during ovulation.**

- **LH (Luteinizing Hormone): the principal surge occurs about 36 hours before ovulation and induces progesterone secretion.**

FSH promotes follicular growth and estradiol production. Ovarian hormones exert negative feedback on gonadotropin secretion:

- **Progesterone inhibits LH release;**
- **Estrogens inhibit FSH secretion.**

GnRH (Gonadotropin-Releasing Hormone) is synthesized by the hypothalamus and released in a pulsatile pattern (two to three pulses per hour), stimulating the secretion of pituitary gonadotropins.

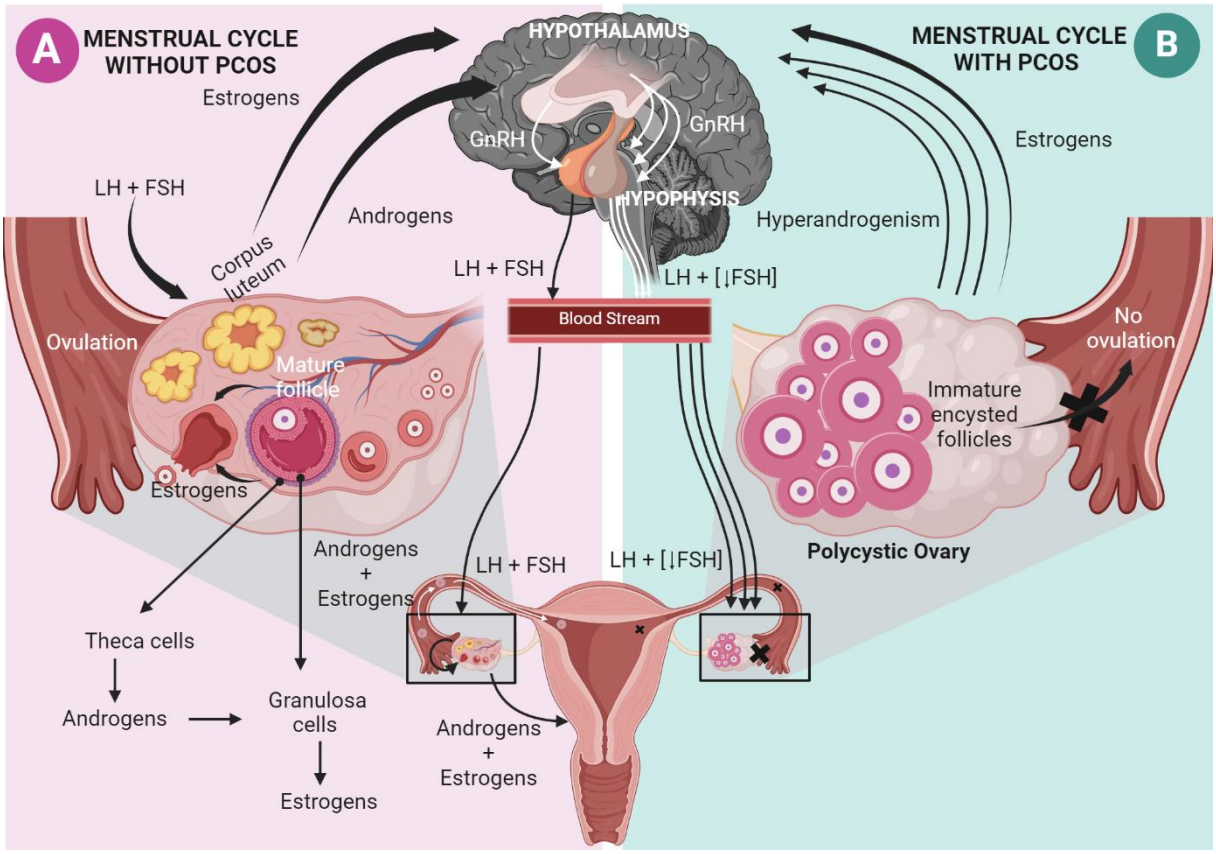

Figure 8: Hormonal Regulation of the Female Reproductive Cycle: The Hypothalamic–Pituitary–Ovarian Axis.