



The Menstrual Cycle

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Question:-

MENSTRUATION; Is it the beginning or the terminal event in menstrual cycle?

The Menstrual Cycle:

Menstrual cycle represents a complex interaction between **hypothalamus, pituitary gland, ovaries and endometrium.**


Hypothalamic-Pituitary Axis:

Pituitary Gland

pituitary gland lies below the hypothalamus at the base of the brain within a bony cavity (sella turcica).

It is divided into two major portions:-

1. **The neurohypophysis**, which consists of the posterior lobe (pars nervosa), the neural stalk (infundibulum), and the median eminence is in direct continuity with the hypothalamus and central nervous system.



○ 2. **The adenohypophysis**, which consist of pars distalis(anterior lobe), pars intermedia (intermediate lobe), & pars tuberalis which surrounds the neural stalk.

○ The arterial blood supply to the median eminence and the neural stalk (pituitary portal system) represents a major avenue of transport for hypothalamic secretions to the anterior pituitary.



○ The anterior pituitary secretes:-

- 1. Follicle –stimulating hormone (FSH).
- 2. luteinizing hormone (LH).
- 3. Thyroid-stimulating hormone (TSH).
- 4. Prolactine.
- 5. Growth hormone (GH).
- 6. Adrenocorticotropic hormne (ACTH).



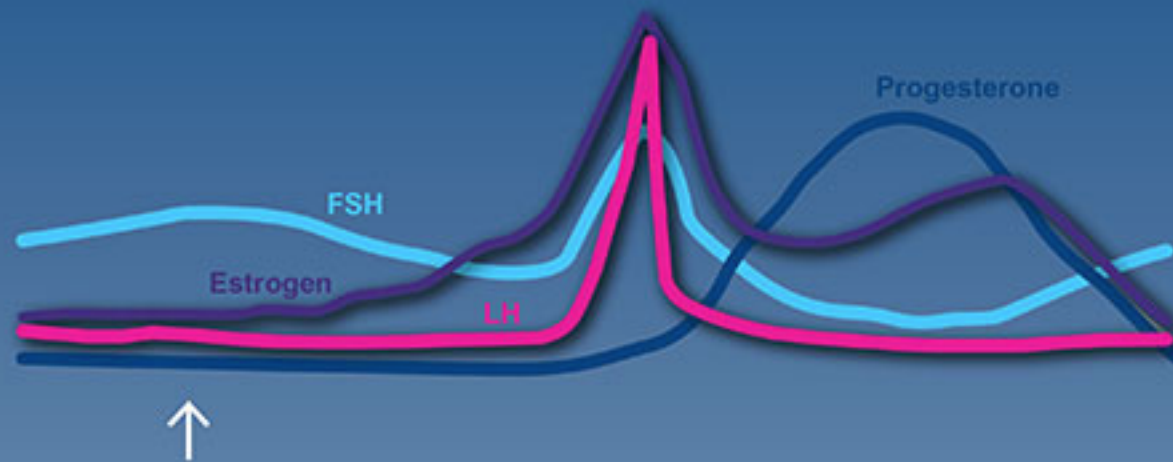
○ FSH and LH, are synthesized and stored in cells called **gonadotrophs**

○ FSH, LH and TSH are glycoproteins consist of α and β sub units.

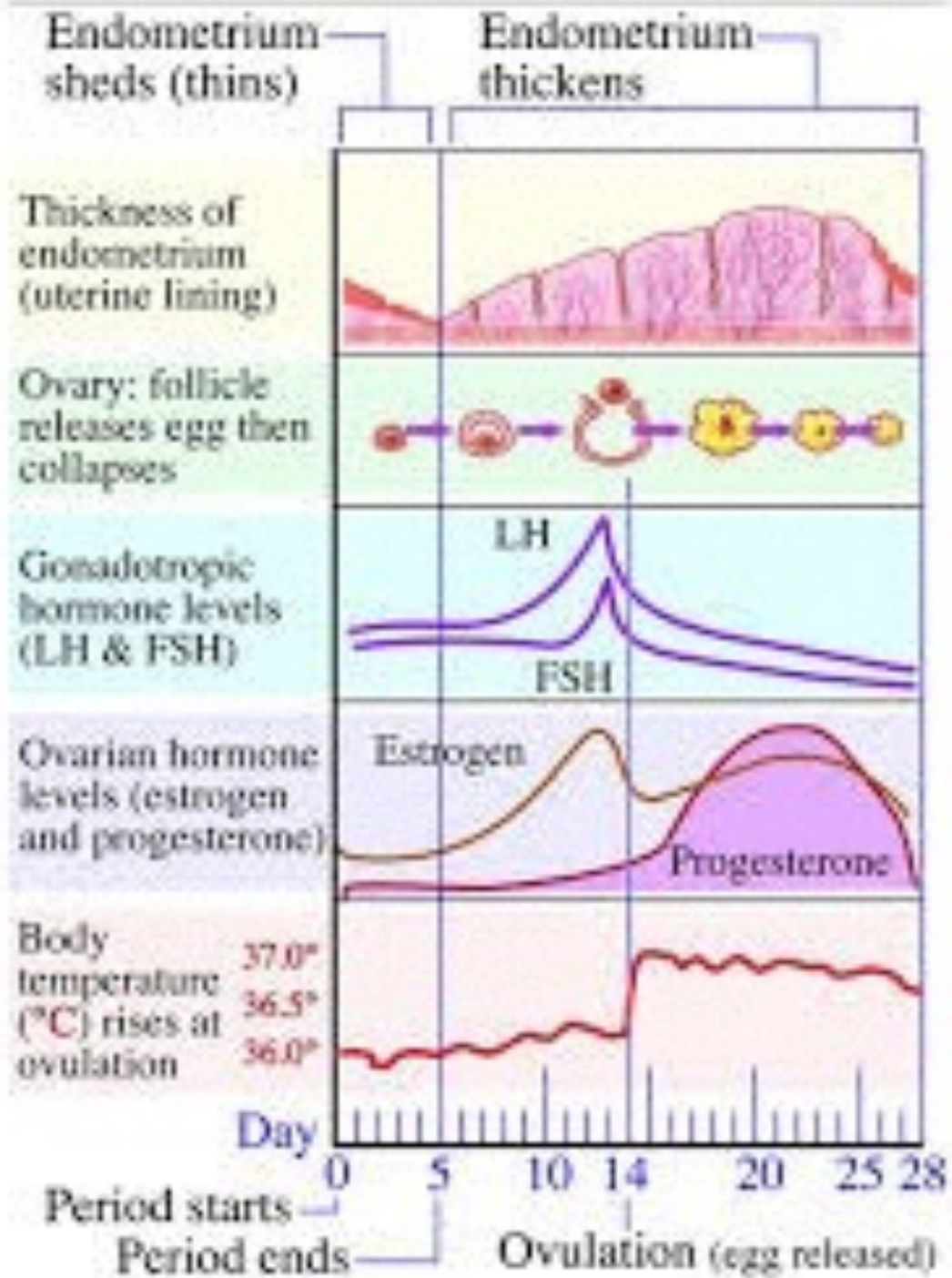
○ The α sub units of FSH, LH, and TSH are identical. **The same α subunits is also present in human chorionic gonadotrophin (hCG).** The β sub units are specific for each hormone

Preparing for Ovulation

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Your body produces hormones which control your menstrual cycle. At the start of your cycle one important hormone is follicle stimulating hormone [FSH]. The rise in FSH stimulates the follicles in your ovaries [fluid filled cavities that each contain one undeveloped egg] to develop and to start to produce another hormone called estrogen.





Gonadotropin Secretory Patterns


- Normal ovulatory cycle divided into a **follicular and luteal phase**. The follicular phase begins with the onset of menses and culminates in the pre ovulatory surge of LH.
- The **Luteal phase** begins with onset of the pre ovulatory LH surge and ends with first day of menses.
- Decreasing levels of estradiol and progesterone in the **regressing corpus luteum** of the preceding cycle initiate an increase in **FSH**.

○ There are separate cellular functions in the ovarian follicle:-

○ LH stimulates the **theca cells** to produce androgens (androstenedione and testosterone).

○ FSH then stimulates the **granulosa cells** to convert these androgens into estrogens (androstenedione to estrone and testosterone to estradiol).

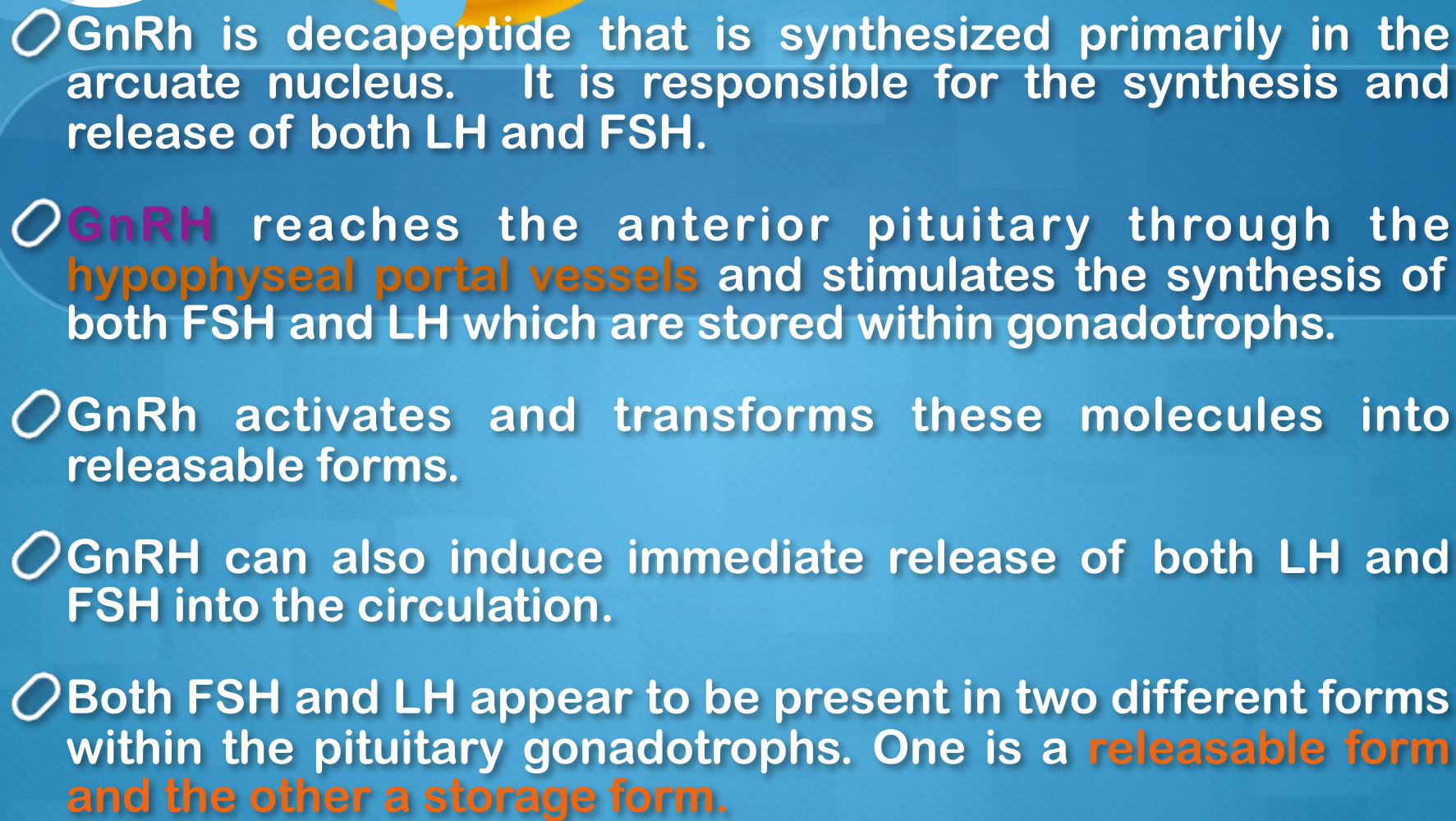
○ Initially, at lower levels of estradiol, there is a negative feedback effect on the ready-release form of LH from the pool of gonadotropins in the pituitary gonadotrophs. As estradiol levels rise later in the follicular phase, there is a positive feedback on the release of storage gonadotropins, resulting in the LH surge and ovulation.

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 - **During the luteal phase**, both LH and FSH are significantly suppressed through the negative feedback effect of elevated circulating estradiol and progesterone.
 - This inhibition persists until progesterone and estradiol levels decline near the end of the luteal phase as a result of corpus luteal regression, if no pregnancy occur.
 - In the beginning of next cycle, there is gradual rise in serum FSH, which initiates new follicular growth.
 - The duration of the corpus luteum's functional regression is **14 days**, after the LH surge in the absence of pregnancy.



Hypothalamus

- Five different small peptides that affect the reproductive cycle have released from hypothalamus.
- All exert specific effects on the hormonal secretion of the anterior pituitary gland.
- They are **GnRH**, **thyrotropin-releasing hormone (TRH)**, somatotropin release-inhibiting factor (SRIF) or **somatostatin**, **corticotropin-releasing factor (CRF)**, and prolactin release-inhibiting factor (PIF).

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- GnRh is decapeptide that is synthesized primarily in the arcuate nucleus. It is responsible for the synthesis and release of both LH and FSH.
 - **GnRH** reaches the anterior pituitary through the **hypophyseal portal vessels** and stimulates the synthesis of both FSH and LH which are stored within gonadotrophs.
 - GnRh activates and transforms these molecules into releasable forms.
 - GnRH can also induce immediate release of both LH and FSH into the circulation.
 - Both FSH and LH appear to be present in two different forms within the pituitary gonadotrophs. One is a **releasable form** and the other a **storage form**.



○ **GnRH** is secreted in a pulsatile fashion throughout the menstrual cycle.

○ The frequency of GnRH release, varies from about every **90 minutes** in the early **follicular** phase to every 60 to **70 minutes** in the immediate **preovulatory** period. **During the luteal phase**, pulse frequency decreases while pulse amplitude increases.

○ A continuous (non pulsatile) infusion of GnRH results in reversible inhibition of gonadotropin secretion through a process of “down regulation” or desensitization of pituitary gonadotrophs.



○ Several mechanism control the secretion of GnRH:-

○ **Estradiol** enhances hypothalamic release of GnRH and may help induce the midcycle **LH surge** by increasing GnRH release or by enhancing pituitary responsiveness to the decapeptide.

○ **Gonadotropins** have inhibitory effect on GNRH.


○ Dopamine has direct inhibitory effect on GNRH.

○ Serotonin inhibit GNRH pulsatile release.

Ovarian Cycle

Estrogens

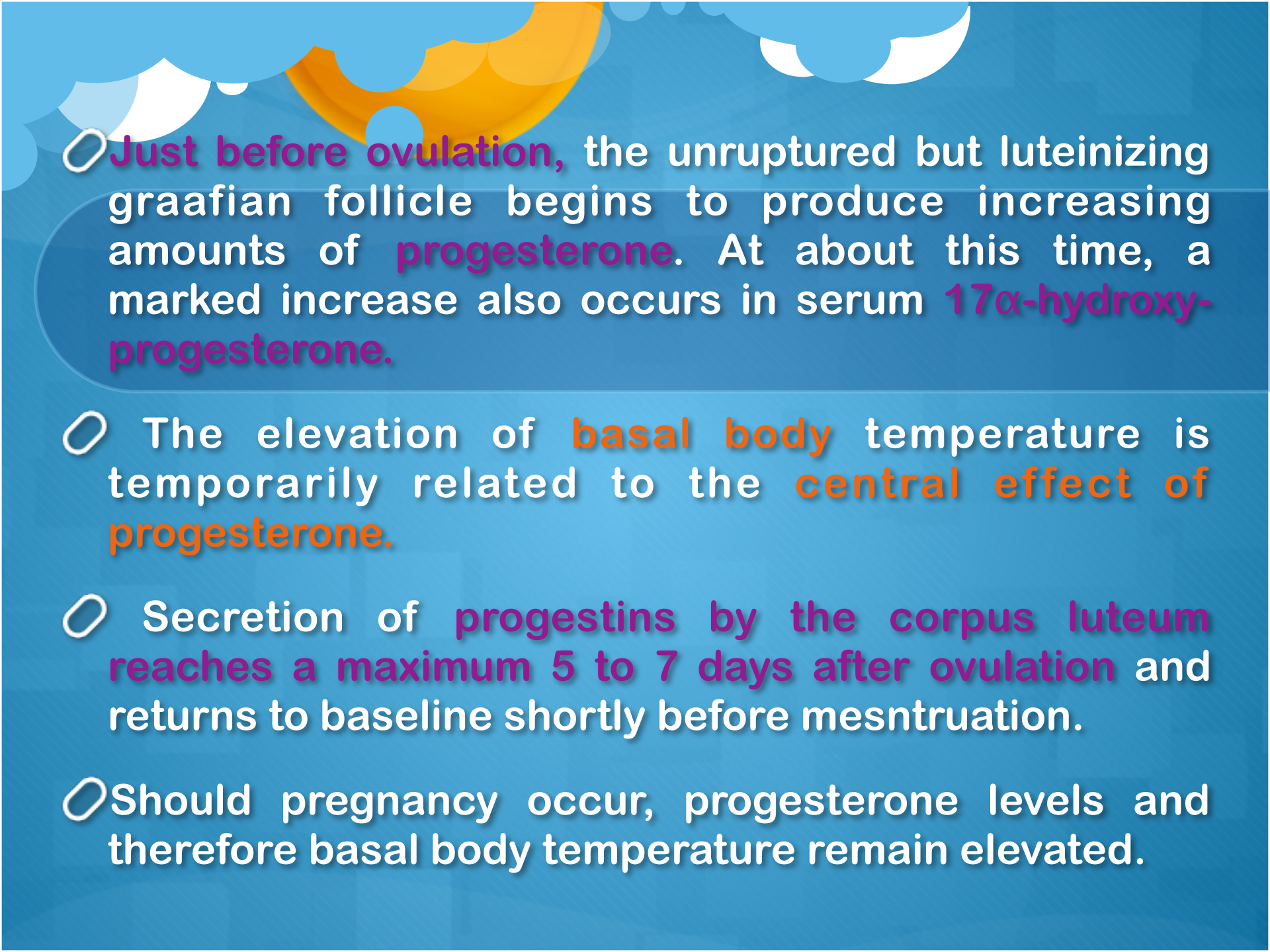
- During **early follicular** development, circulating estradiol levels are relatively **low**.
- About **1 week before ovulation**, levels begin to increase, at first slowly, then rapidly. The conversion of testosterone to estradiol in the granulosa cell of the follicle occurs through an enzymatic process called aromatization .
- The levels reach a **maximum 1 day before the midcycle LH peak**.

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- After this peak and before ovulation, there is a marked and precipitous fall.
 - During **luteal phase**, estradiol rises to a **maximum 5 to 7 days after ovulation** and returns to baseline shortly before menstruation.
 - Estrone secretion by the ovary is considerably less than secretion of estradiol but follows a similar pattern.
 - Estrone is largely derived from the conversion of androstenedione through the action of the enzyme aromatase.



PROGESTINS

- **During follicular development**, the ovary secretes only **very small amounts** of progesterone and 17α -hydroxyprogesterone.
- **The bulk** of the progesterone comes from the **peripheral conversion** of adrenal pregnenolone and pregnenolone sulfate.



○ **Just before ovulation**, the unruptured but luteinizing graafian follicle begins to produce increasing amounts of **progesterone**. At about this time, a marked increase also occurs in serum **17 α -hydroxy-progesterone**.

○ The elevation of **basal body** temperature is temporarily related to the **central effect of progesterone**.

○ Secretion of **progestins** by the **corpus luteum** reaches a maximum 5 to 7 days after ovulation and returns to baseline shortly before menstruation.

○ Should pregnancy occur, progesterone levels and therefore basal body temperature remain elevated.

ANDROGENS

- Both the ovary and the adrenal glands secrete small amounts of testosterone.
- but most of the testosterone is derived from the **metabolism of androstenedione**, which is also secreted by both the ovary and the adrenal gland.
- Near midcycle, an increase occurs in plasma androstenedione, due to enhanced secretion from the follicle.
- During the luteal phase, a **second rise** occurs in androstenedione, which reflects enhanced secretion by the **corpus luteum**.
- The **adrenal gland** also secretes androstenedione in a **diurnal** pattern similar to that of cortisol.



○ The ovary secretes small amounts of the very potent dihydrotestosterone (DHT), but the bulk of DHT is derived from the conversion of androstenedione and testosterone.

○ The majority of dehydro-epiandrosterone (DHEA) and virtually all DHEA sulfate (DHEA-S), which are weak androgens, are secreted by the adrenal glands.

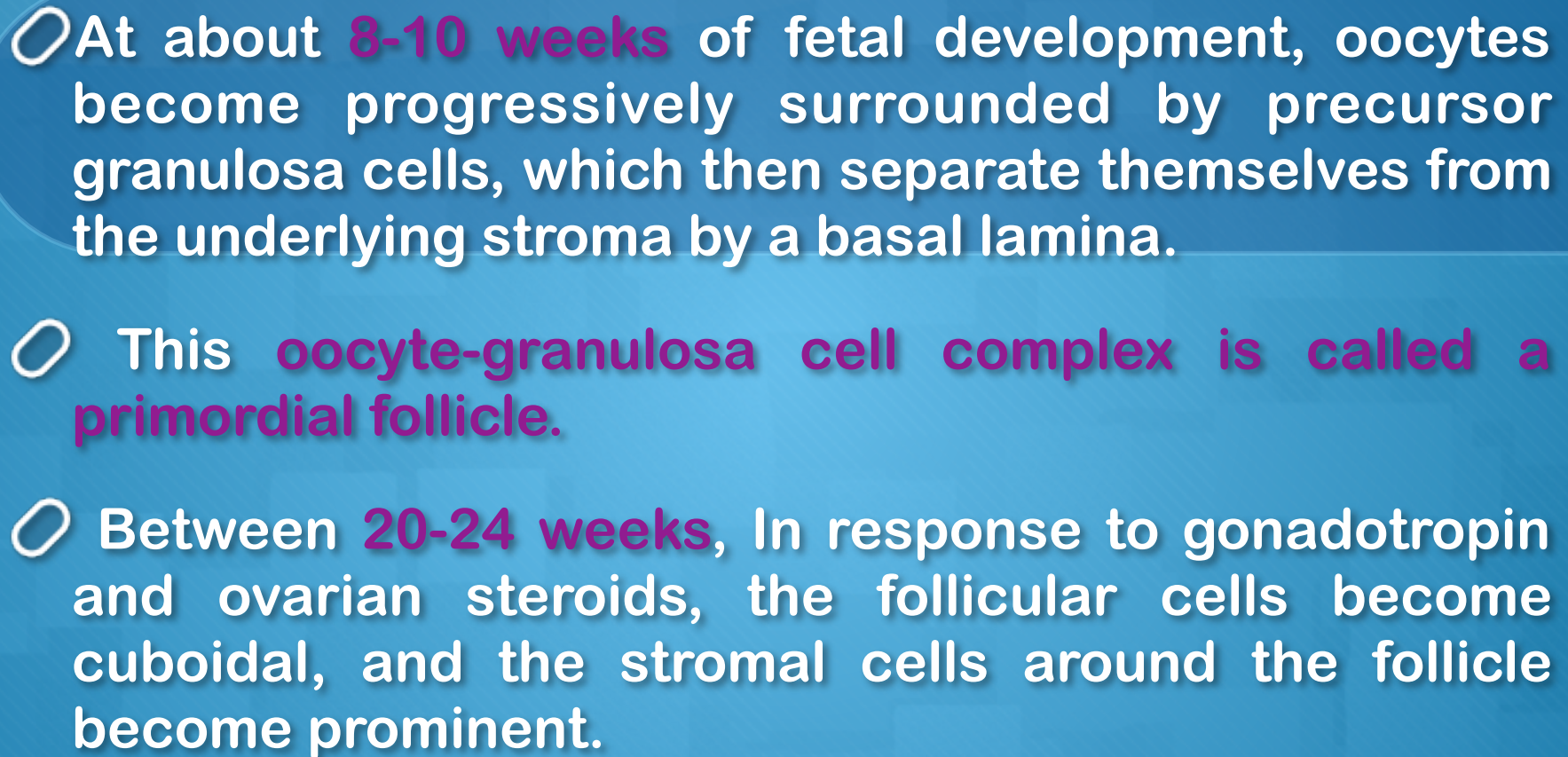
Serum-Binding Proteins

- Circulating estrogens and androgens are mostly bound to specific **sex hormone-binding globulins (SHBG)** or to serum albumin.
- The remaining fraction of sex hormones is **unbound (free)**, and this is the **biologically active** fraction.
- The synthesis of SHBG in the **liver** is increased by **estrogens and thyroid hormones** but decreased by **testosterone**.

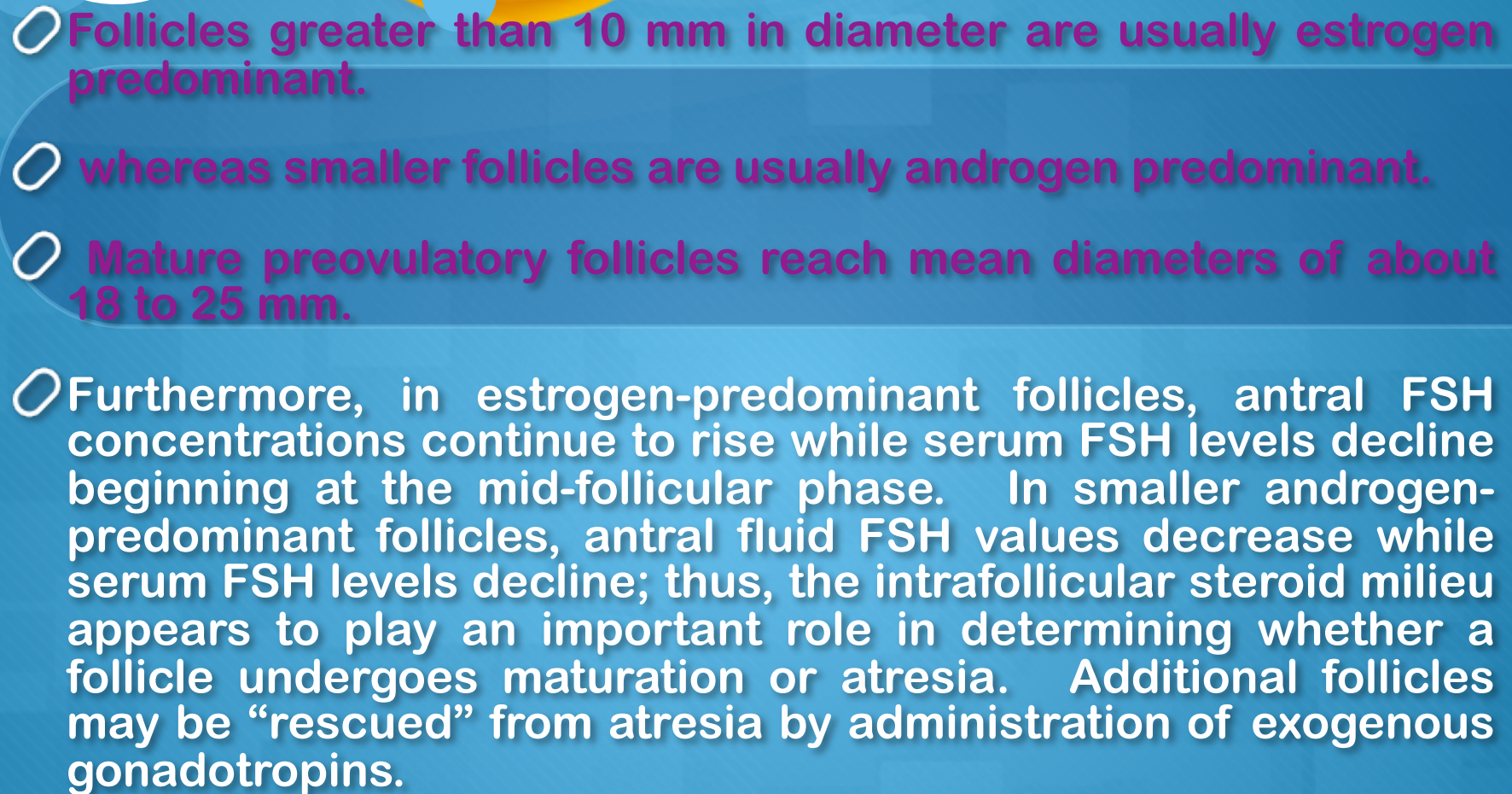



Follicular Development

- Primordial follicles undergo sequential development, differentiation, and maturation until a **mature graafian follicle is produced.**
- The follicle then ruptures, releasing the ovum. Subsequent luteinization of the ruptured follicle produces the **corpus luteum.**

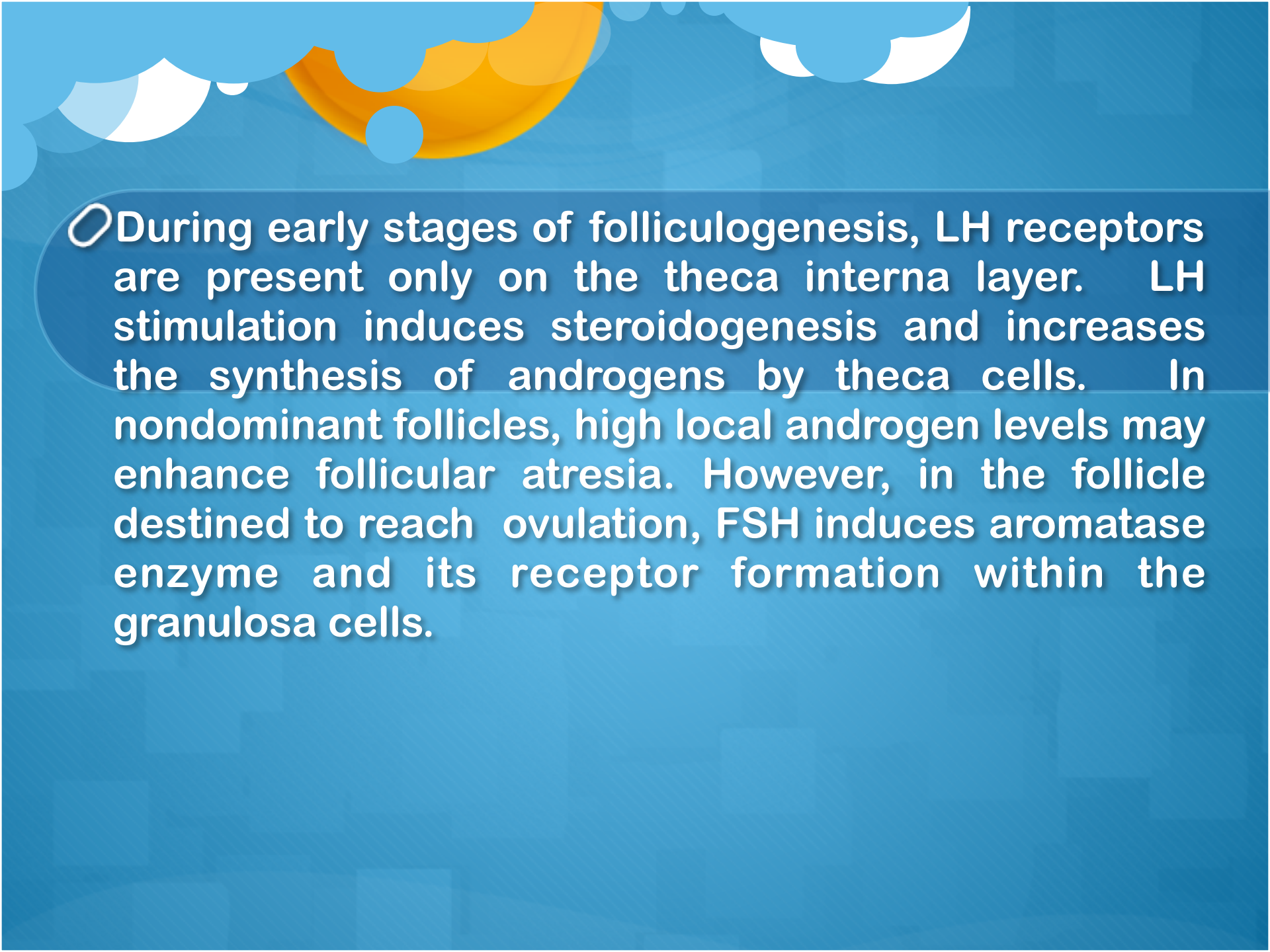
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- At about **8-10 weeks** of fetal development, oocytes become progressively surrounded by precursor granulosa cells, which then separate themselves from the underlying stroma by a basal lamina.
 - This **oocyte-granulosa cell complex** is called a **primordial follicle**.
 - Between **20-24 weeks**, In response to gonadotropin and ovarian steroids, the follicular cells become cuboidal, and the stromal cells around the follicle become prominent.

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- During each cycle, a cohort follicles is recruited for development.
 - Among the many developing follicles, only **one usually continues differentiation and maturation into a follicle that ovulates.**
 - The remaining follicles undergo atresia.


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- Follicles greater than 10 mm in diameter are usually estrogen predominant.
 - whereas smaller follicles are usually androgen predominant.
 - Mature preovulatory follicles reach mean diameters of about 18 to 25 mm.
 - Furthermore, in estrogen-predominant follicles, antral FSH concentrations continue to rise while serum FSH levels decline beginning at the mid-follicular phase. In smaller androgen-predominant follicles, antral fluid FSH values decrease while serum FSH levels decline; thus, the intrafollicular steroid milieu appears to play an important role in determining whether a follicle undergoes maturation or atresia. Additional follicles may be “rescued” from atresia by administration of exogenous gonadotropins.



○ Follicular maturation is dependent on the local development of receptors for FSH and LH. FSH receptors are present on granulosa cells. Under FSH stimulation, granulosa cells proliferate, and the number of FSH receptors per follicle increases proportionately. Thus, the growing primary follicle is increasingly more sensitive to stimulation by FSH; as a result, estradiol levels increase. Estrogens, particularly estradiol enhance the induction of FSH receptors and act synergistically with FSH to increase LH receptors.



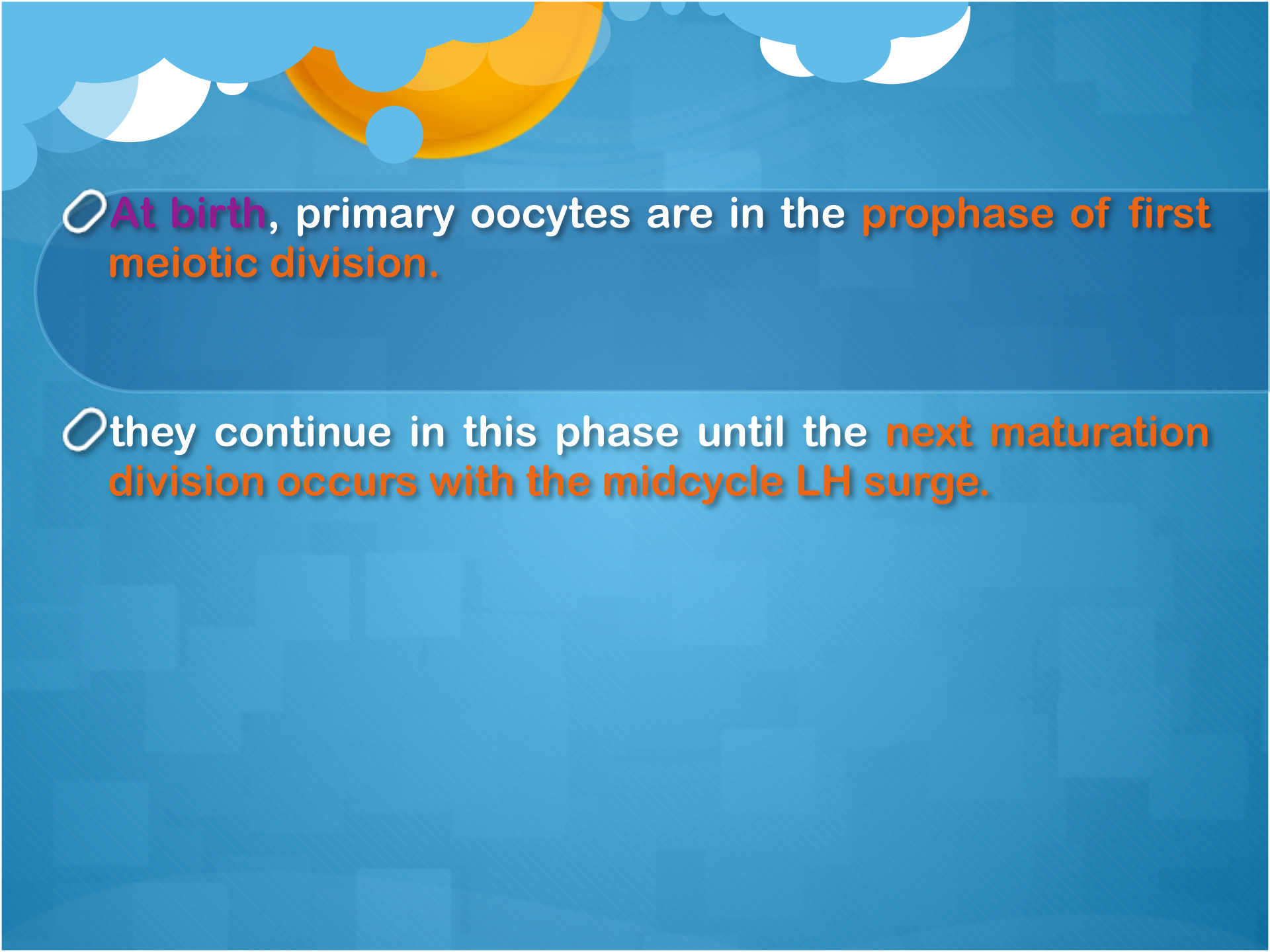
○ During early stages of folliculogenesis, LH receptors are present only on the theca interna layer. LH stimulation induces steroidogenesis and increases the synthesis of androgens by theca cells. In nondominant follicles, high local androgen levels may enhance follicular atresia. However, in the follicle destined to reach ovulation, FSH induces aromatase enzyme and its receptor formation within the granulosa cells.

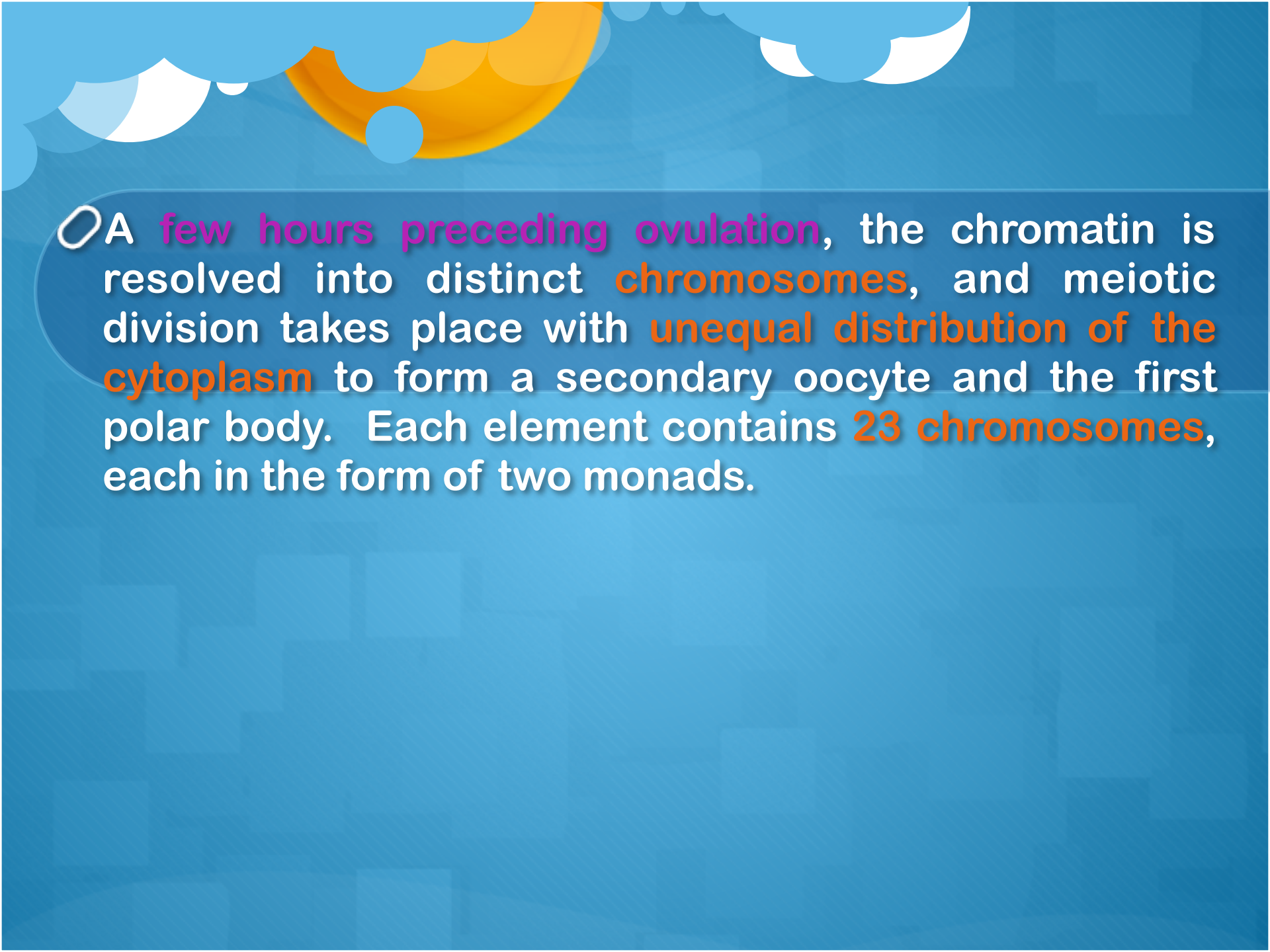


○ As a result, androgens produced in the theca interna of the dominant follicle diffuse into the granulosa cells and are aromatized into estrogens. FSH also enhances the induction of LH receptors on the granulosa cells of the follicle that is destined to ovulate.

Ovulation:

- The ovulatory LH surge initiates a sequence of structural and biochemical changes that leads to ovulation.
- Before ovulation, a general dissolution of the entire follicular wall occurs, particularly the portion that is on the surface of the ovary. This occurs as a result of the action of **proteolytic enzymes**.
- With degeneration of the cells on the surface, a stigma forms, and the follicular basement membrane finally bulges through the stigma. When this ruptures, the oocyte, together with the corona radiata and some cumulus oophora cells, is expelled into the peritoneal cavity.

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- At birth, primary oocytes are in the **prophase of first meiotic division**.
 - they continue in this phase until the **next maturation division occurs with the midcycle LH surge**.



○ A few hours preceding ovulation, the chromatin is resolved into distinct **chromosomes**, and meiotic division takes place with **unequal distribution of the cytoplasm** to form a secondary oocyte and the first polar body. Each element contains **23 chromosomes**, each in the form of two monads.

Luteinization and Corpus Luteum

Function

- After ovulation and under the influence of LH, the granulosa cells of the ruptured follicle undergo luteinization.
- These luteinized granulosa cells, plus the surrounding theca cells, capillaries, and connective tissue, form the corpus luteum, which produces copious amounts of progesterone and some estradiol.
- The normal functional duration of the corpus luteum is 9 -10 days.
- It regresses if no pregnancy occurs, menstruation starts, and the corpus luteum is gradually replaced by an avascular scar called a corpus albicans.

Histopathology of the Endometrium

○ Functionally, the endometrium is divided into two zones:

○ 1. The **outer portion**, or **functionalis**, that undergoes cyclic changes in morphology and function during the menstrual cycle and is sloughed off at menstruation; and

○ 2. The **inner portion**, or **basalis**, that remains relatively unchanged during each menstrual cycle and, after menstruation, provides stem cells for the renewal of functionalis.

○ **Basal arteries** are regular blood vessels found in the basalis, whereas **spiral arteries** are especially coiled blood vessels seen in the functionalis.



The cyclic changes in histophysiology of the endometrium can be divided into three stages:

○ The menstrual phase.

○ The proliferative or estrogenic phase.

○ The secretory or progestational phase.


Menstrual Phase

- Because it is the only portion of the cycle that is visible externally, the first day of menstruation is taken as **day 1 of the menstrual cycle**.
- During this phase, there is disruption and disintegration of the endometrial glands and stroma, leukocyte infiltration, and red blood cell extravasation.
- In addition to this sloughing of the functionalis, there is a compression of the basalis due to the loss of ground substances.



Proliferative Phase

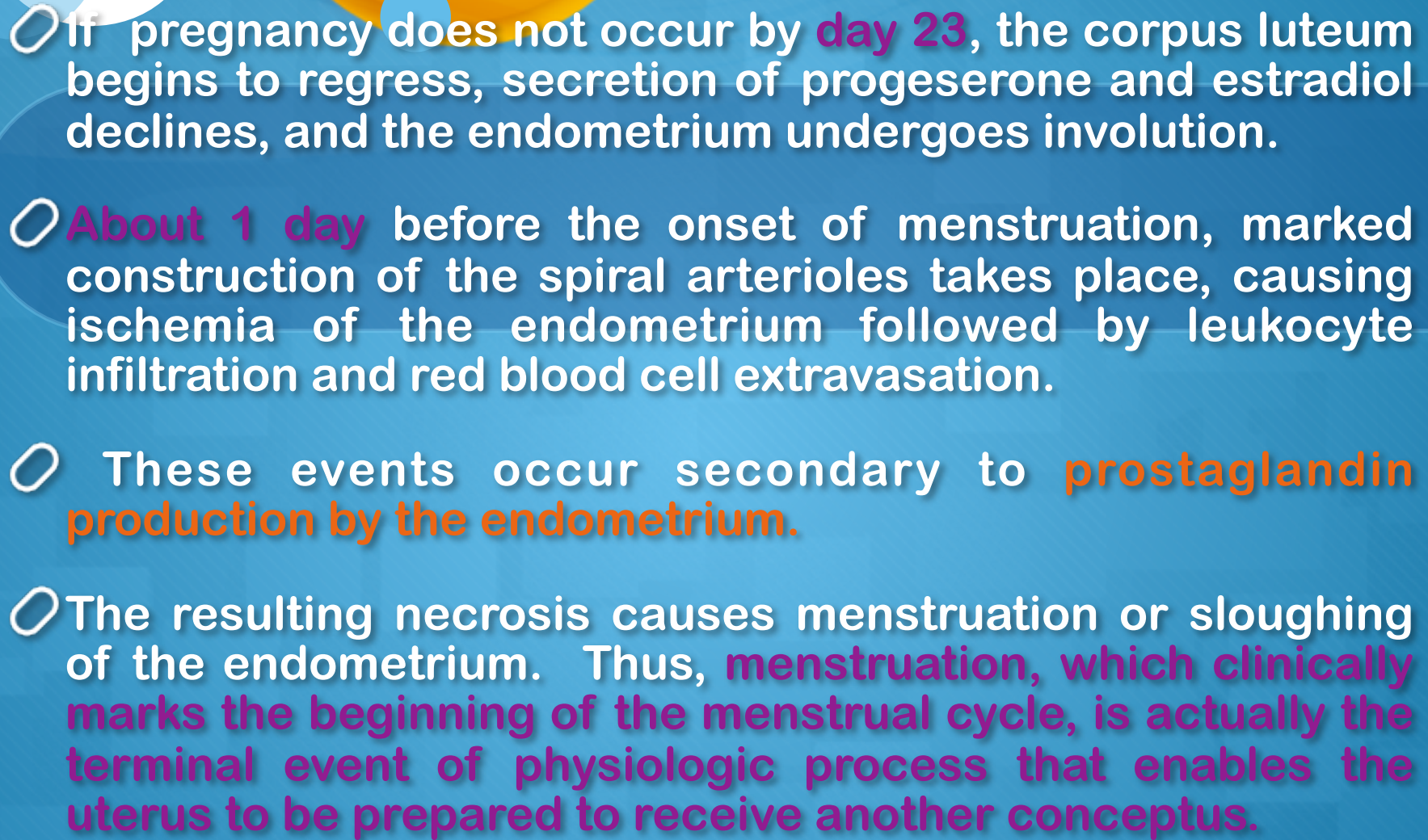
- The proliferative phase is characterized by endometrial growth secondary to estrogenic stimulation.
- Because the bases of the endometrial glands lie deep within the basalis, these epithelial cells are not destroyed during menstruation.
- During this phase of the cycle, the large increase in estrogen secretion causes marked cellular proliferation of the epithelial lining, the endometrial glands, and the connective tissue of the stroma.

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- Numerous mitoses are present in these tissues, and there is an increase in the length of the spiral arteries, which traverse almost the entire thickness of the endometrium.
 - By the end of the proliferative phase, cellular proliferative and endometrial growth have reached a maximum, the spiral arteries are elongated and convoluted, and the endometrial glands are straight, with narrow lumens containing some glycogen.



Secretory Phase

- **Following ovulation**, progesterone secretion by the corpus luteum stimulates the glandular cells secrete **glycogen**, mucus, and other substances.
- The **glands become tortuous** and the lumens are dilated and filled with these substances. The stroma becomes edematous. Mitoses are rare.
- The **spiral arteries continue to extend into the superficial layer of the endometrium** and become convoluted.

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- If pregnancy does not occur by **day 23**, the corpus luteum begins to regress, secretion of progesterone and estradiol declines, and the endometrium undergoes involution.
 - **About 1 day** before the onset of menstruation, marked constriction of the spiral arterioles takes place, causing ischemia of the endometrium followed by leukocyte infiltration and red blood cell extravasation.
 - These events occur secondary to **prostaglandin production by the endometrium**.
 - The resulting necrosis causes menstruation or sloughing of the endometrium. Thus, **menstruation, which clinically marks the beginning of the menstrual cycle, is actually the terminal event of physiologic process that enables the uterus to be prepared to receive another conceptus.**

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