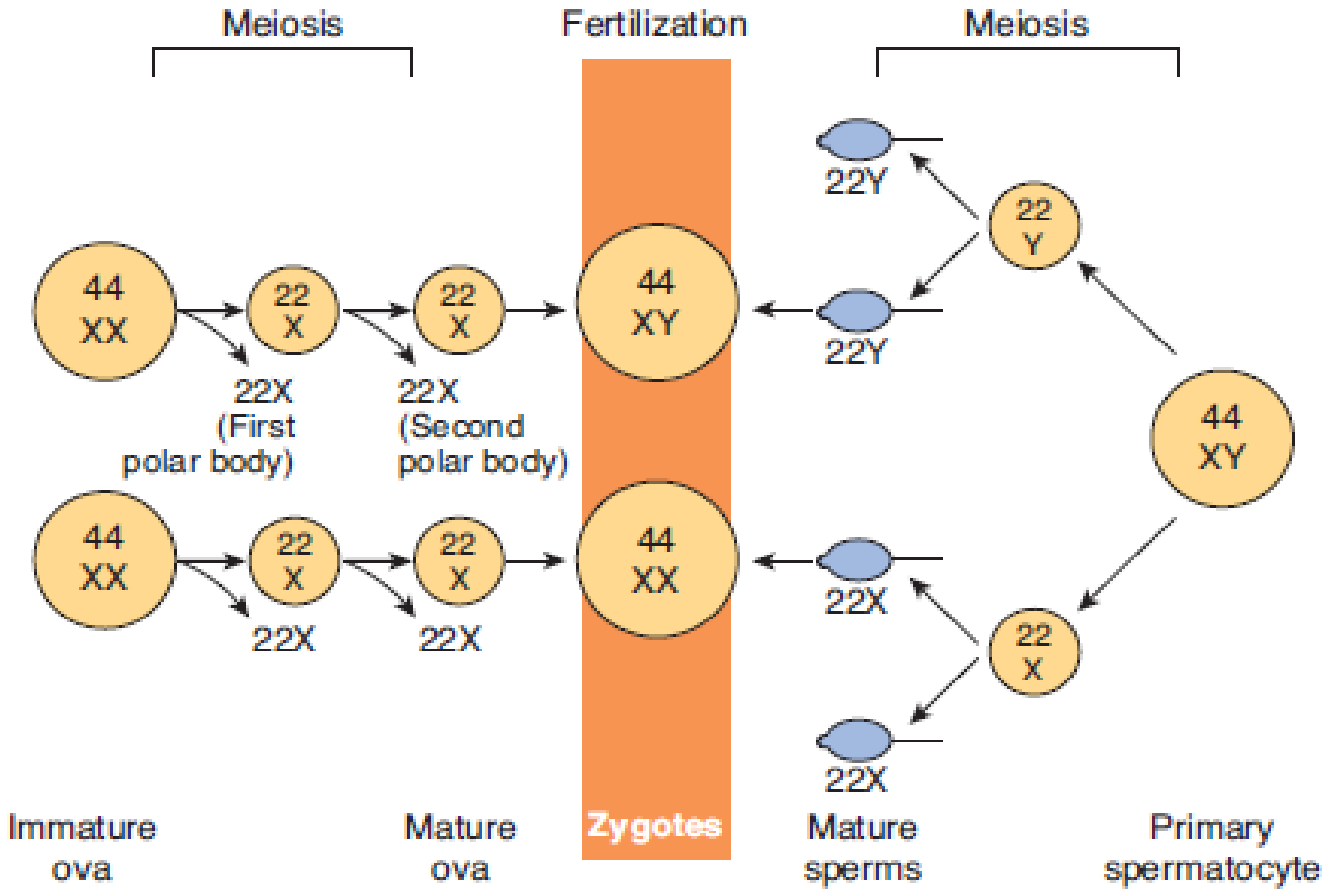
# DASAR-DASAR BIOMOLEKULER REPRODUKSI WANITA

## Kuliah 2

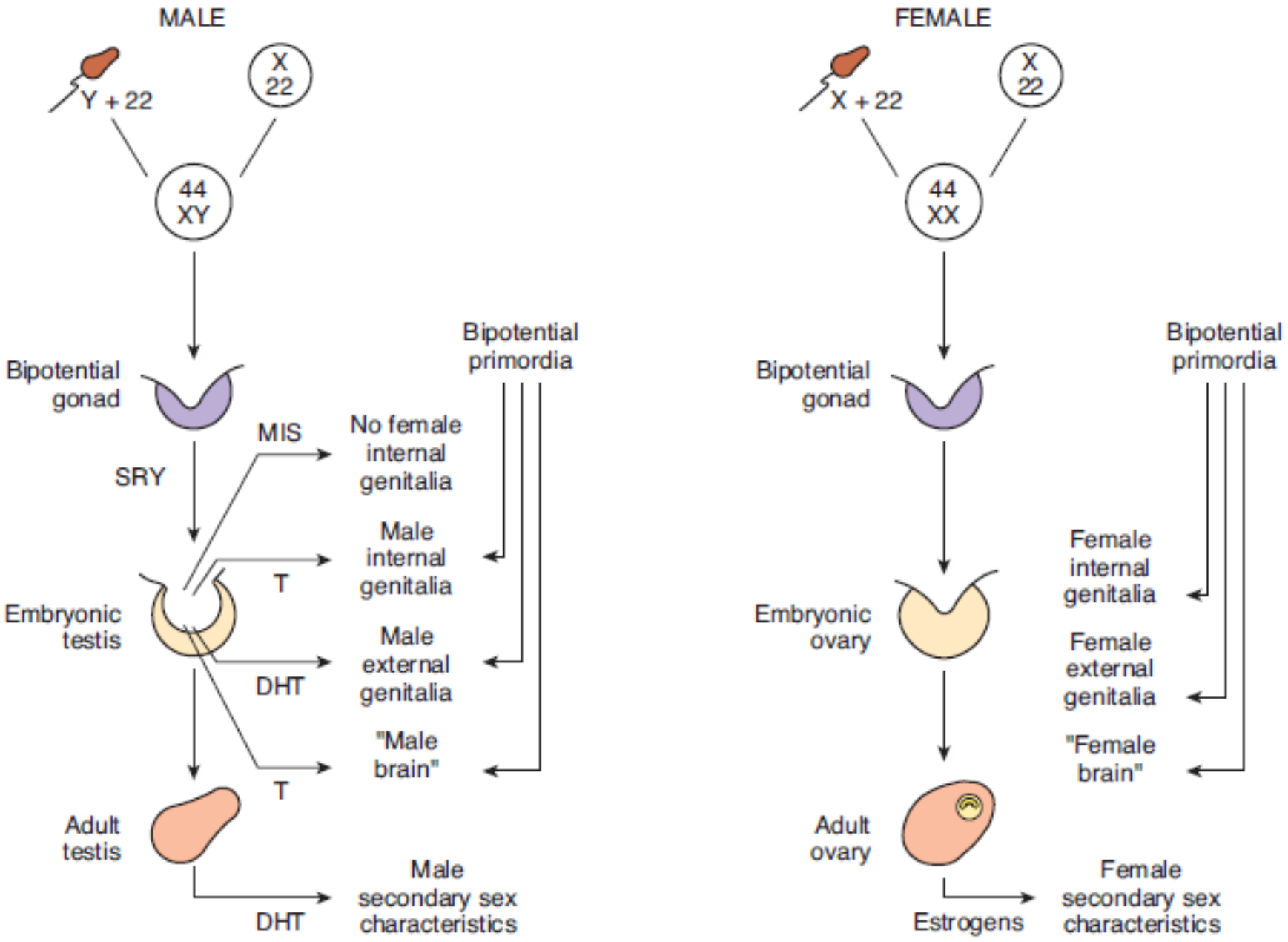
**Rahmatina B. Herman**
**Bagian Fisiologi**
**Fakultas Kedokteran Universitas Andalas**

# Sex Determination and Differentiation

- Reproductive cells/gamete each contain a half set of chromosomes (haploid)
- Gametogenesis is accomplished by meiosis
- The sex of and individual is determined by combination of sex chromosomes
- Sexual differentiation along male or female lines depends on the presence/absence of masculinizing determinant




**Basis of genetic sex determination.**




**Diagrammatic summary of normal sex determination, differentiation, and development in humans.**

**Ovaries does not secrete hormone and factor**

**Absence of testosterone**

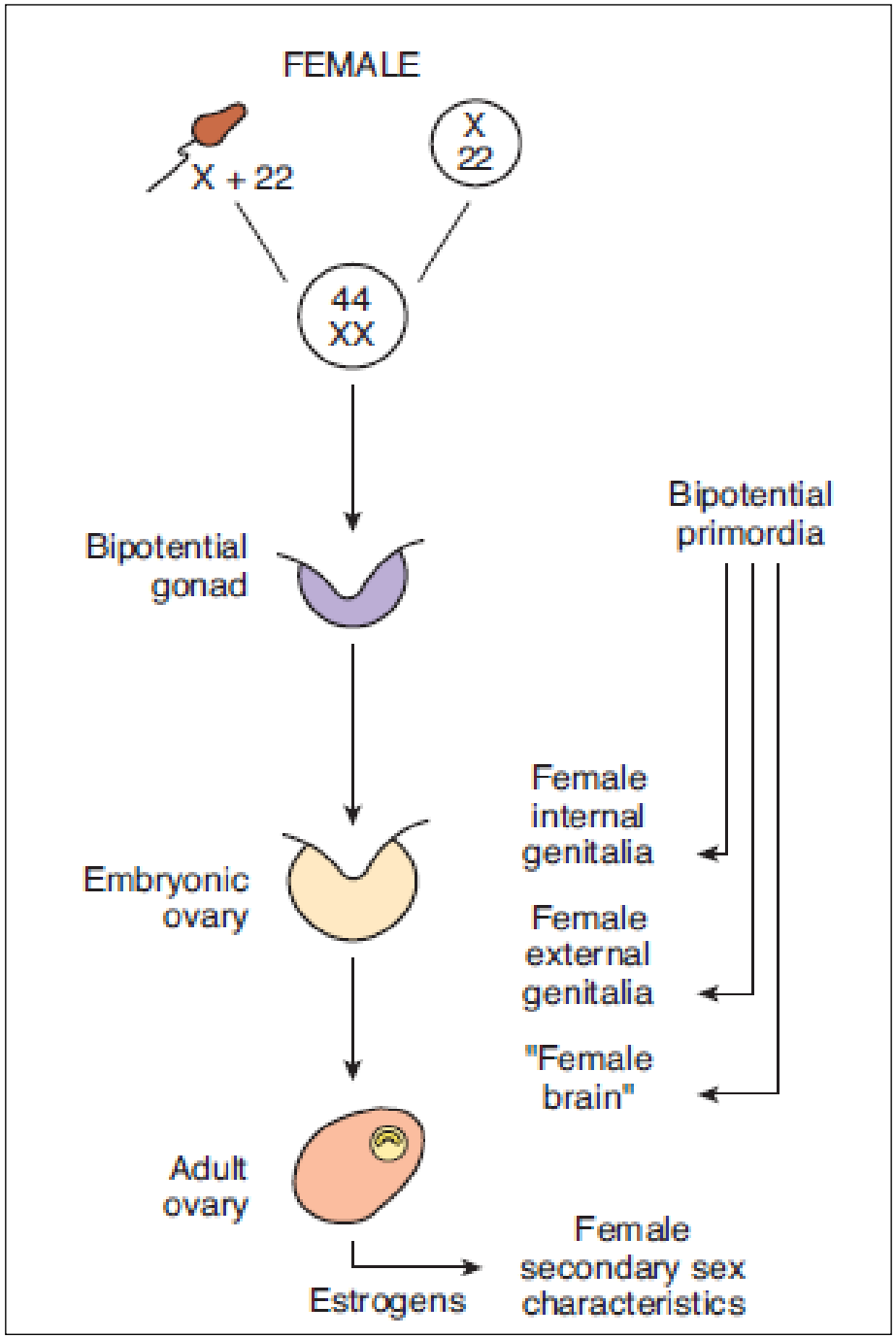
**Degeneration of Wolfian ducts**

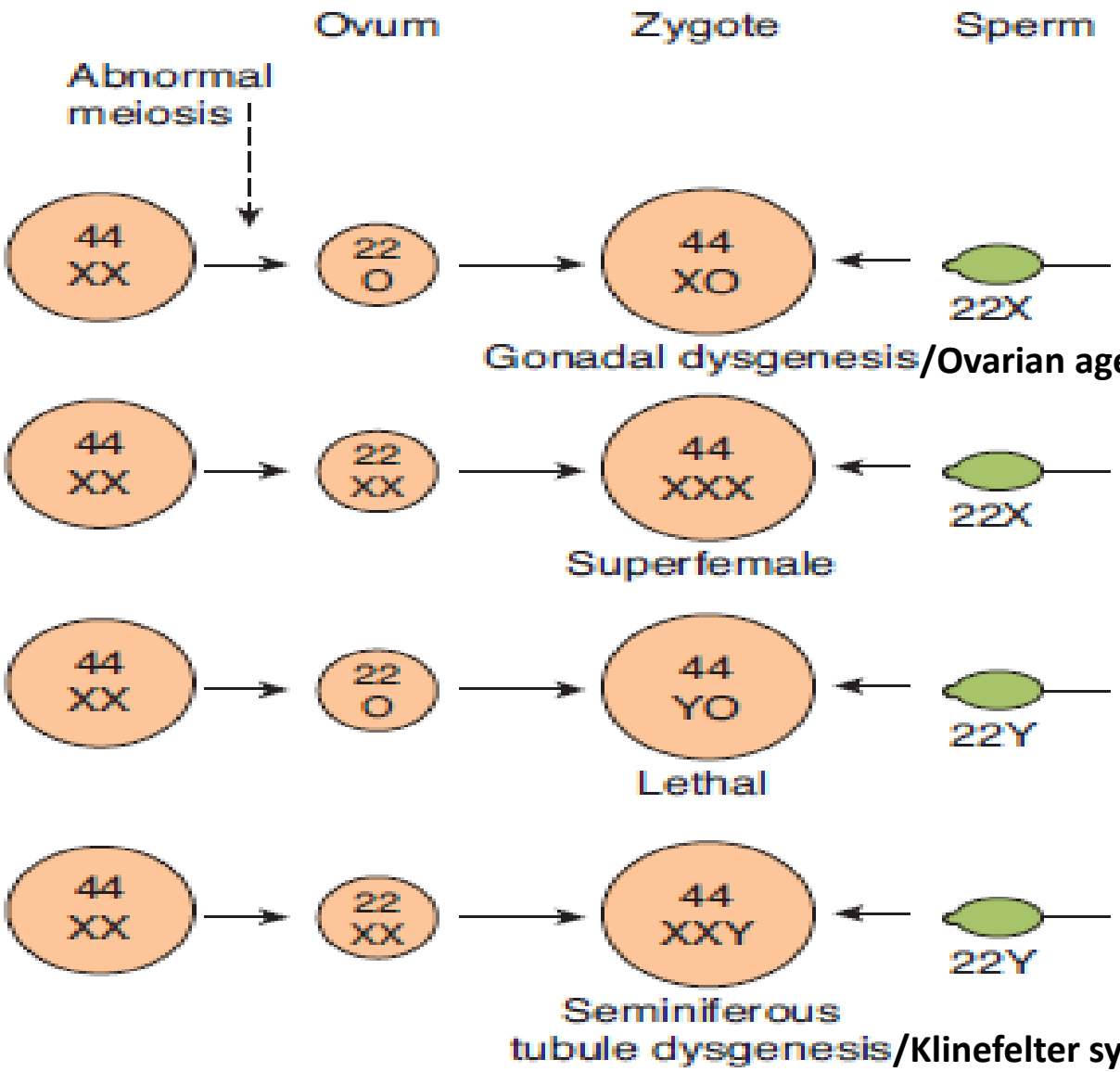
**Absence of Mullerian-inhibiting factor**

**Undifferentiated external genitalia along female lines (e.g. clitoris. labia)**

**Mullerian ducts develop Into female reproductive tract (e.g. oviducts, uterus)**

**Phenotype sex**






**Summary of 4 possible defects produced by maternal nondisjunction of sex chromosomes at the time of meiosis**

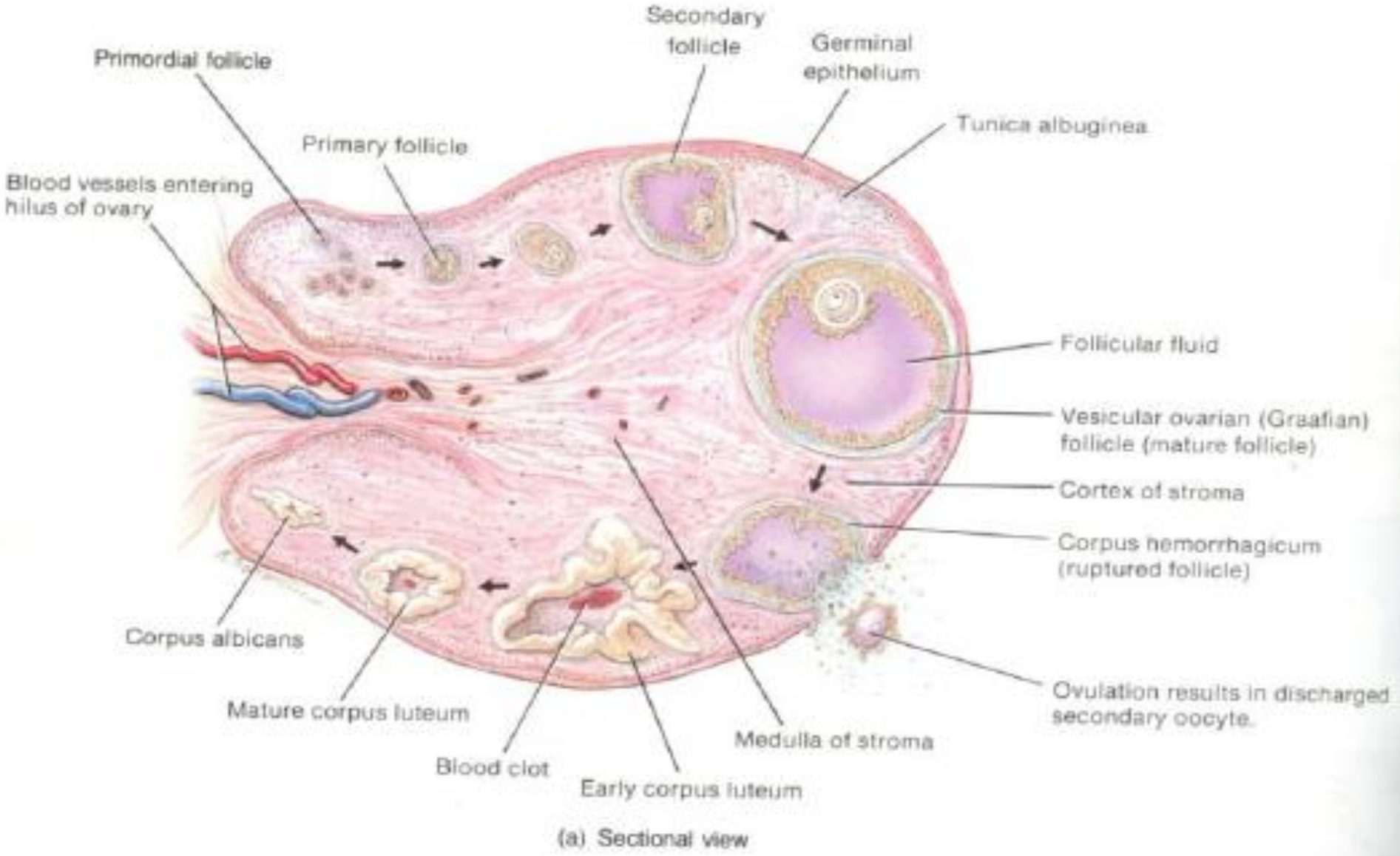
**The YO combination is believed to be lethal, the fetus dies in utero**

# Female Reproductive System

- Reproductive system of women shows regular cyclic changes that may be regarded as periodic preparation for fertilization and pregnancy
- In humans and primate, the cycle is a menstrual cycle and its conspicuous feature is periodic vaginal bleeding that occurs with the shedding of uterine mucosa (menstruation)
- In other mammal: the sexual cycle is called estrous cycle, no episodic vaginal bleeding occurs, but the underlying endocrine events are essentially similar
  - in some species: ovulation occurs spontaneously
  - in other species: ovulation is induced by copulation (reflex ovulation)

# Ovaries

- **Primary female reproductive organs**
- **Perform dual function:**
  - **producing ova (oogenesis)**
  - **secreting female sex hormones:**
    **estrogen and progesterone which act together to:**
    - **> promote fertilization of ovum**
    - **> prepare female reproductive system for pregnancy**
- **Containing various levels of follicle development**




**Histology of the ovary. The arrows indicate the sequence of developmental stages that occur as part of ovarian cycle**

# Oogenesis

- Undergo numerous mitotic divisions
- ± 7 month after conception, fetal oogonia cease dividing

  From this point on, no new germ cells are generated
- Still in the fetus, all oogonia develop into primary oocytes

# Primary Oocyte

- Begin a first meiotic division by replicating their DNA
- However, they do not complete the division in the fetus
- Accordingly, all the eggs present at birth are primary oocytes containing 46 chromosomes, each with two sister chromatids
- Cells are said to be in a state meiotic arrest
  State meiotic arrest continues until puberty and the onset of renewed activity in ovaries
- Only primary oocytes destined for ovulation will ever complete the first meiotic division, for it occurs just before the egg is ovulated

# Primary Oocyte…..

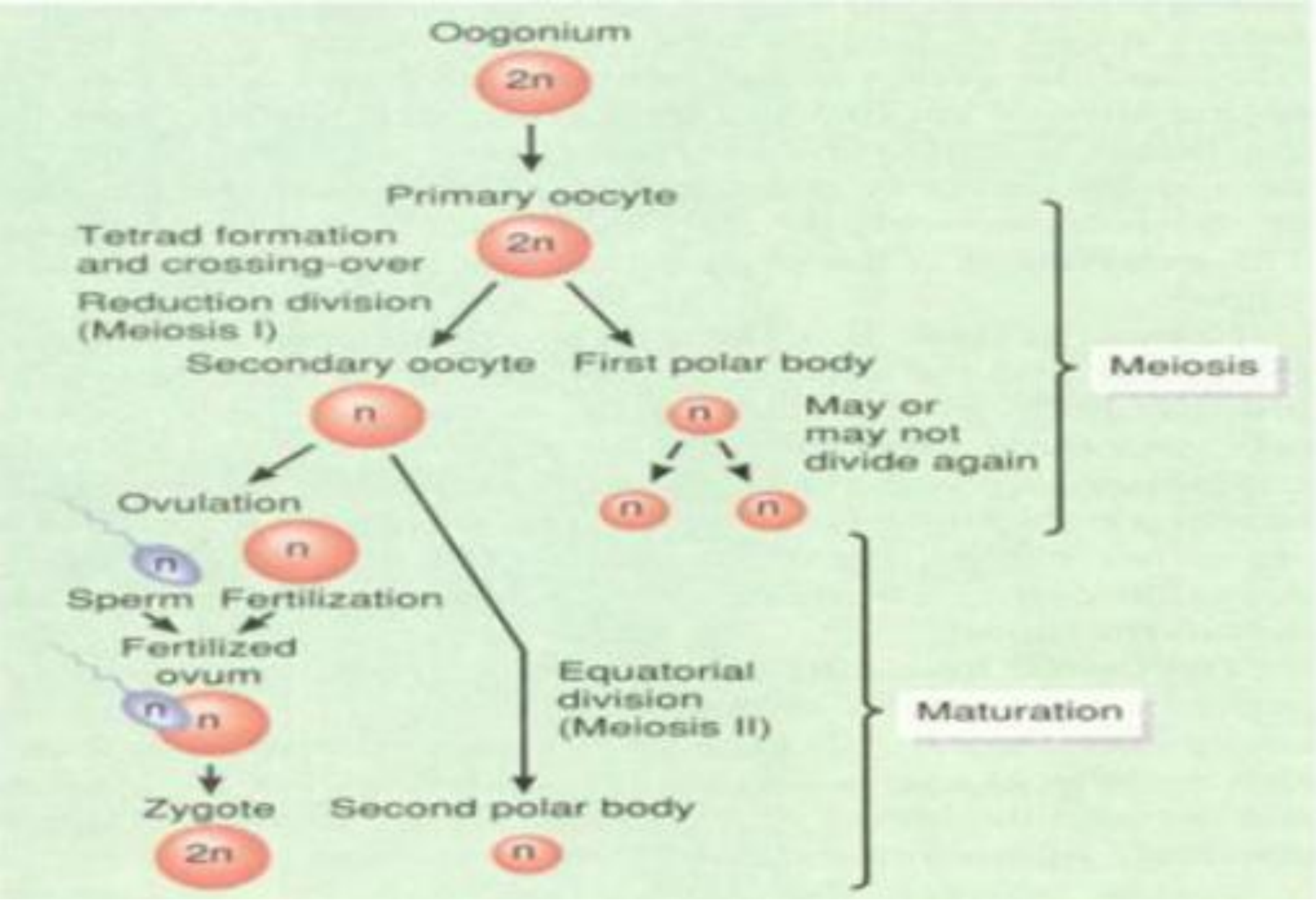
- Each daughter cells receives 23 chromosomes, each with 2 chromatids
- One of the two daughter cells, secondary oocytes retains virtually all cytoplasm (other is first polar body)
- Thus, the primary oocytes:
  - Already as large as the egg will be
  - Passes on to be secondary oocyte half of its chromosomes but almost all of its nutrient-rich cytoplasm

# Secondary Oocyte

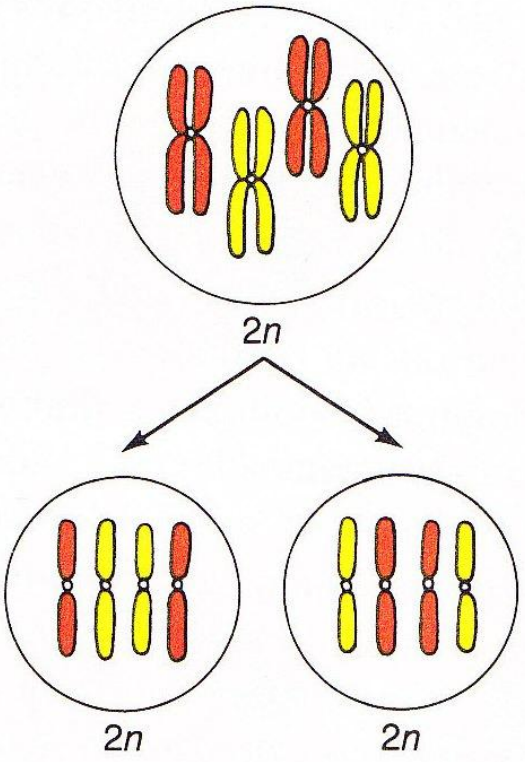
- The second meiotic division occurs in a fallopian tube after ovulation, but only if the secondary oocyte is fertilized (penetrated by a sperm)
- Daughter cells each receive 23 chromosomes, each with a single chromatid
- One of the two daughter cells, termed an ovum retains nearly all cytoplasm (other is second polar body)

# Final Result of Oogenesis

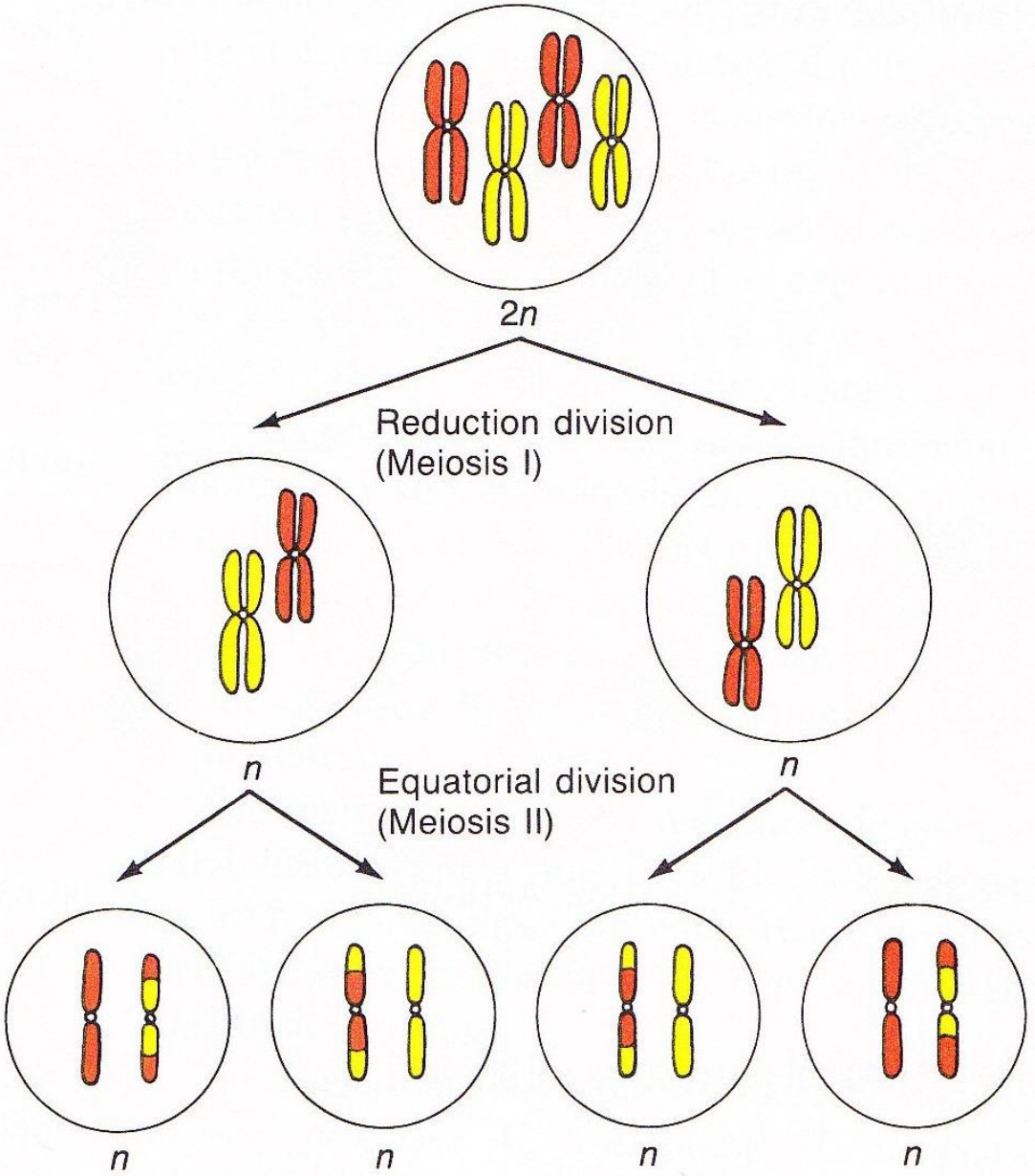
- **Net result of oogenesis is that each primary oocyte can produce only one ovum**




**Oogenesis. 2n means diploid (46 chromosomes; n means haploid (23 chromosomes)**

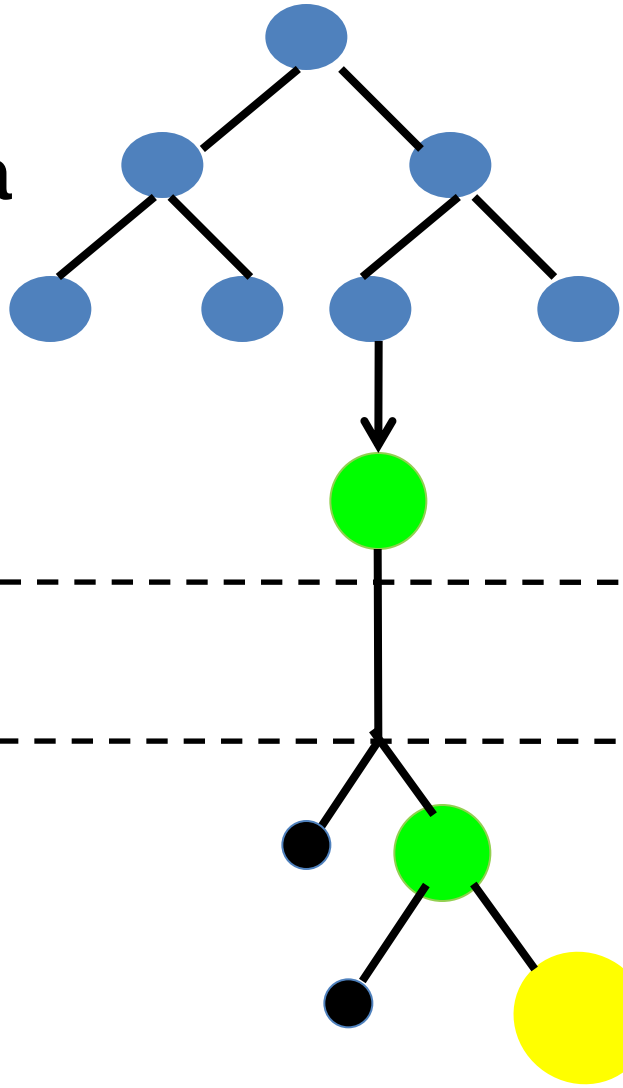



(a) Mitosis




(b) Meiosis

# Summary of Oogenesis



Oogonia

Birth

Puberty

| | Chromosomes Per cell | Chromatids Per cell |
|---|---|---|
| Oogonia | 46 | 2 |
| Birth | 46 | 2 |
| Puberty | 23 | 2 |
| | 23 | 1 |

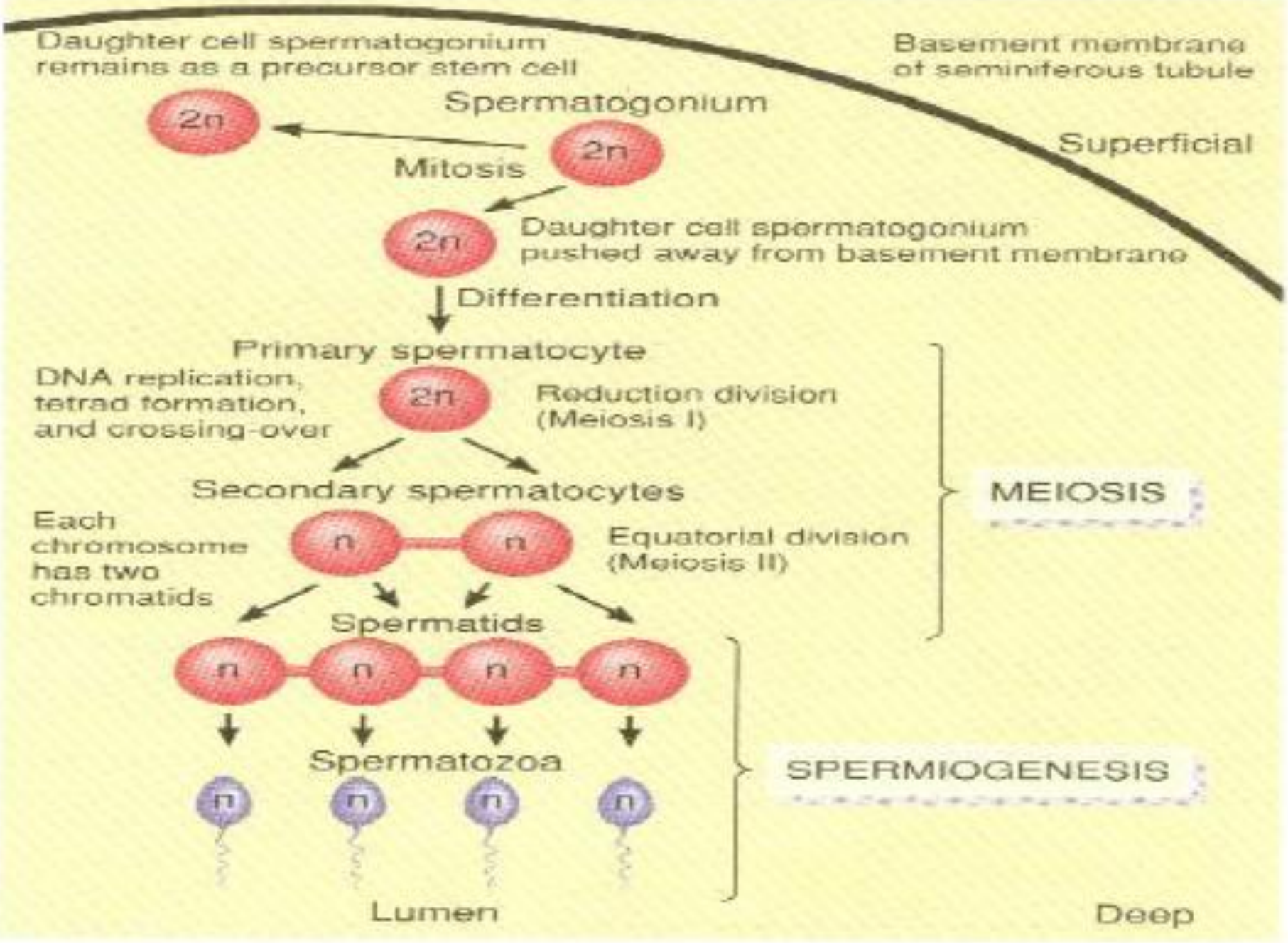
# Summary of Oogenesis…..

- **Oogonia: mitotic divisions until ± 7 month after conception**
- **Mitosis of oogonium → primary oocyte**
- **Meiosis of primary oocyte, but do not complete (beginning of the 1st meiotic division) → meiotic arrest**
- **Primary oocyte at birth containing 46 chromosomes**
- **1st meiotic division is completed just before ovulation → secondary oocyte**
- **2nd meiotic division occurs in a fallopian tube after ovulation, but only if the secondary oocyte is fertilized (penetrated by a sperm)**

# Comparison of Spermatogenesis and Oogenesis

## Spermatogenesis

- Three major stages:
  1. Mitotic proliferation
  2. Meiosis
  3. Packaging/ spermiogenesis: physically reshaping/ remodeling
- ± 64 days, from spermatogonium to mature sperm
- Up to several hundred million sperm may reach maturity daily


Daughter cell spermatogonium remains as a precursor stem cell
Basement membrane of seminiferous tubule
Spermatogonium
2n
Mitosis
2n
Superficial
2n
Daughter cell spermatogonium pushed away from basement membrane
Differentiation
Primary spermatocyte
DNA replication, tetrad formation, and crossing-over
2n
Reduction division (Meiosis I)
Secondary spermatocytes
Each chromosome has two chromatids
n
n
Equatorial division (Meiosis II)
MEIOSIS
Spermatids
n
n
n
n
Spermatozoa
n
n
n
n
SPERMIOGENESIS
Lumen
Deep

# Follicle

- From the time of birth, there are many primordial follicles, each containing 1 primary oocyte
- Progression of some primordial follicles to preantral and early antral stages occurs
  - throughout infancy and childhood, and
  - then during the entire menstrual cycle
- Therefore, although most of follicles in ovaries are still primordial, there are also always present a relatively constant few number of preantral and early antral follicles

# Menstrual Cycle

- At the start of each menstrual cycle, 10-25 the follicles begin to develop into larger follicles
- In humans, usually one of the larger follicles in one ovary starts to grow rapidly on ± the 6$^{th}$day, becomes the dominant follicle
- The dominant follicle continues to develop, and others (in both ovaries) regress and become a degenerative process called atresia (an example of programmed cell death, or apoptosis)
- The eggs in the degenerating follicles also die

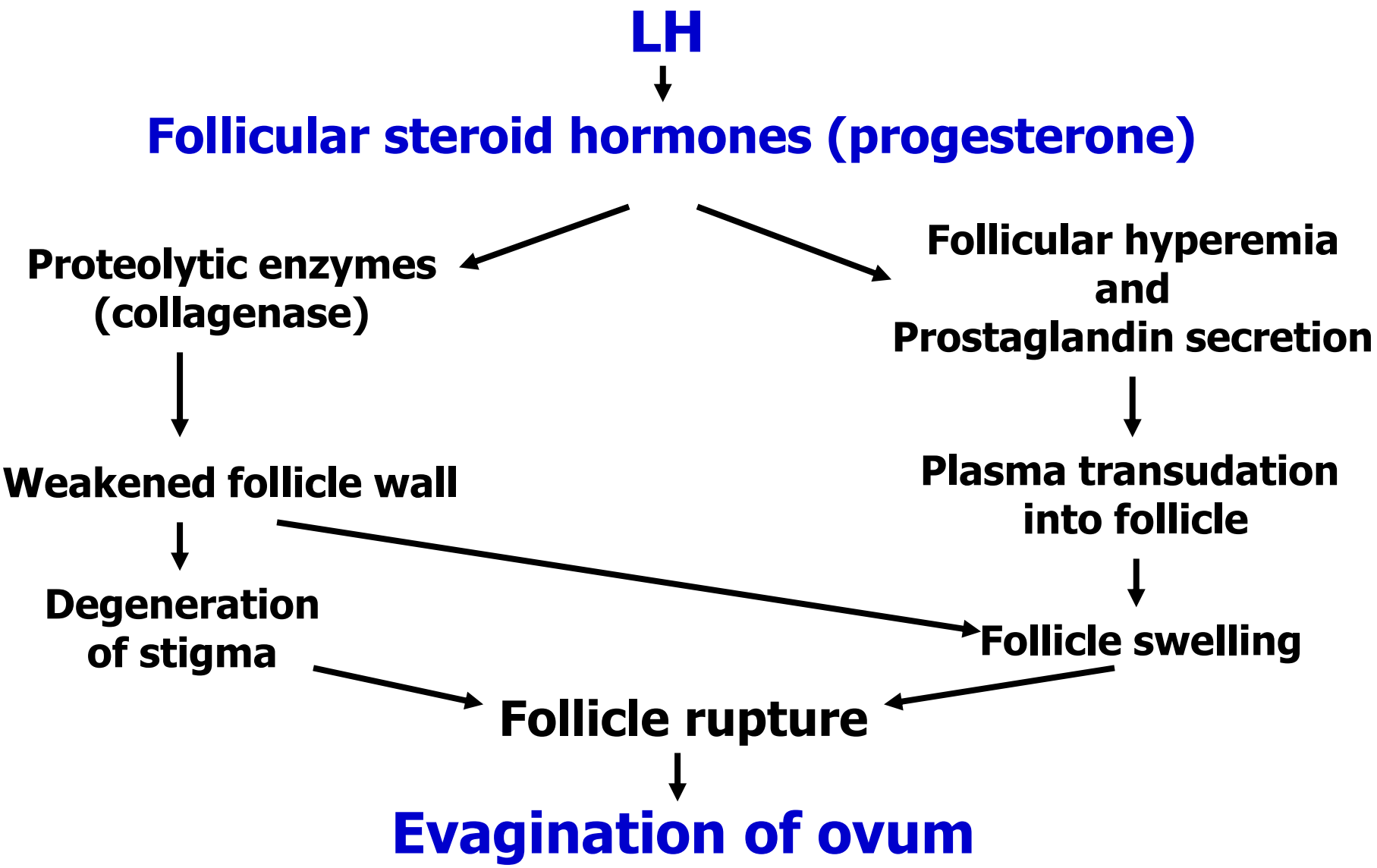
# Ovulation

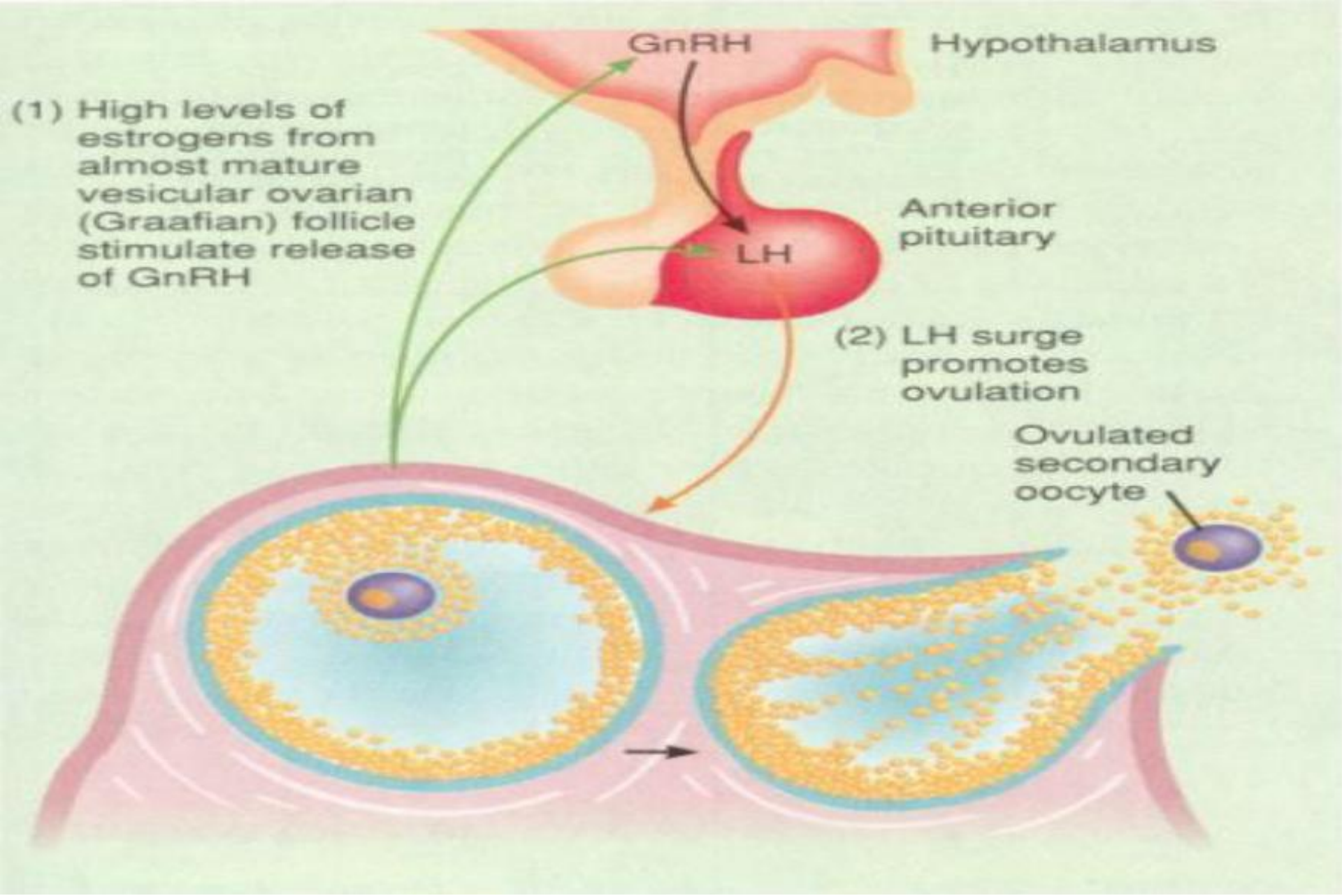
- Mature follicle (Graafian follicle): ± 1,5 cm in diameter, that it balloons out on ovary's surface
- Ovulation occurs when the thin walls of follicle and ovary at site where they are joined rupture because of enzymatic digestion
- Secondary oocyte surrounded by its tightly adhering zona pellucida and granulosa cells, as well as cumulus, is carried out of ovary and onto ovarian surface by antral fluid

# Ovulation…..

- Occasionally, 2 or more follicles reach maturity and more than 1 egg may be ovulated
- This is the most common of cause of multiple births
- In such cases, siblings are fraternal, not identical, because the eggs carry different sets of genes

# Postulated mechanism of ovulation (H. Lipner)






**Positive feedback of high levels of estrogens on secretion of GnRH and LH**

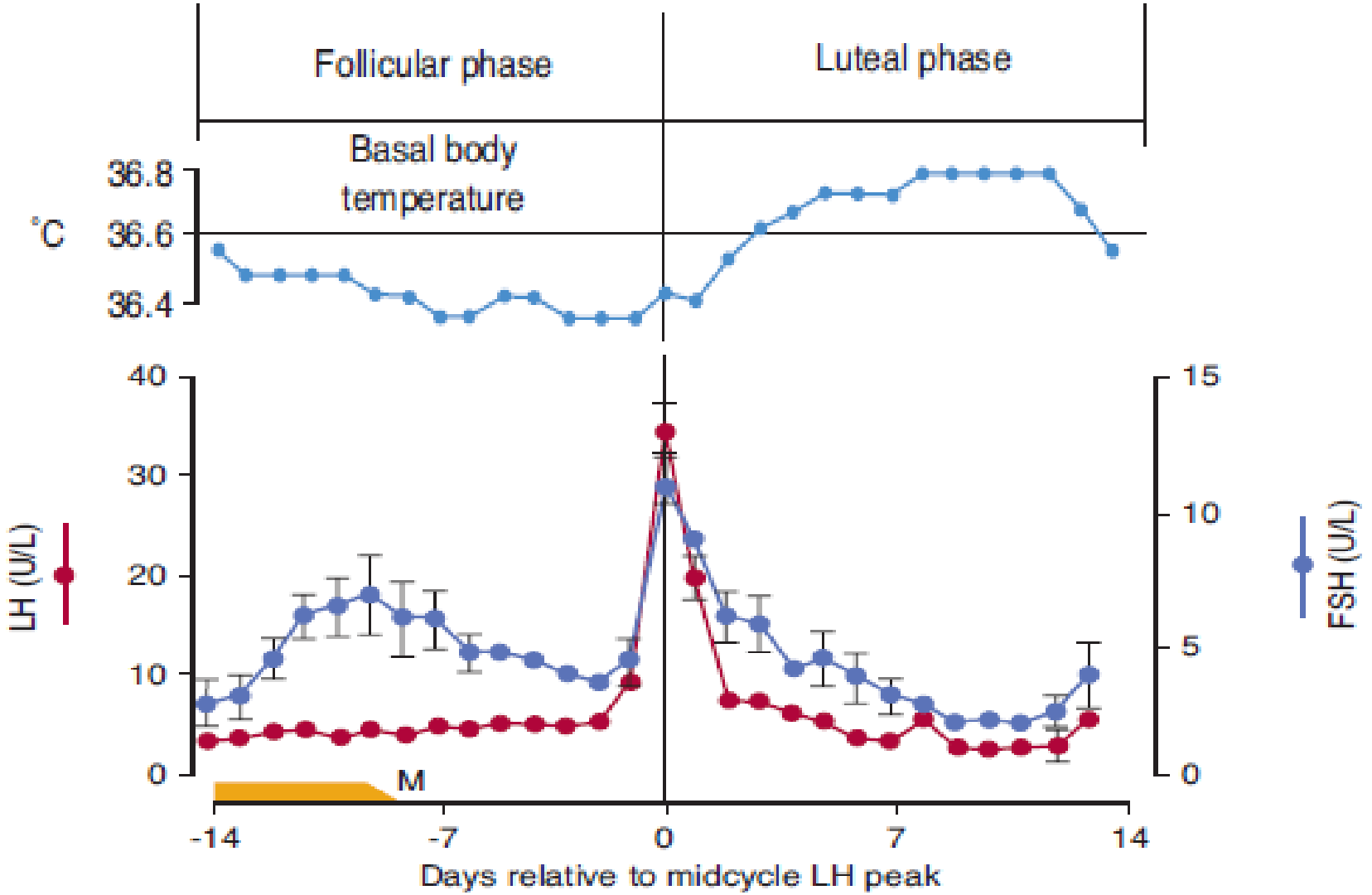
# Indicators of Ovulation

- **A surge in LH secretion triggers ovulation**
  - **Ovulation normally occurs ± 9 h after the peak of LH surge**
  - **The ovum lives for ± 72 h after ovulation, but it is fertilizable for a much shorter time**

    **Research shows:**
    - **> Intercourse on the day of ovulation: pregnancy 36%**
    - **> Intercourse on days after ovulation: pregnancy 0**
    - **> Intercourse 1-2 d before ovulation: pregnancy 36%**
    - **> A few pregnancies resulted from intercourse 3-5 d before ovulation (8% on day 5 before ovulation)**
  - **Thus, some sperms can survive in the female genital tract and fertilize the ovum for up to 120 h before ovulation, but the most fertile period is clearly 48 h before ovulation**

# Indicators of Ovulation…..

- A change (usually rise) in basal body temperature caused by secretion of progesterone, since progesterone is thermogenic
  - The rise starts 1-2 d after ovulation
  - Obtaining an accurate temperature chart should use a digital thermometer and take oral/rectal temperatures in the morning before getting out of bed
  - Temperature change at the time of ovulation is probably caused by the increase in progesterone secretion




**Basal body temperature and plasma LH and FSH concentrations (mean ± SE) during the normal human menstrual cycle**

# Formation of Corpus Luteum

- After mature follicle discharges its antral fluid and egg, it collapses around antrum and undergoes rapid transformation
- Granulosa cells enlarge greatly, and entire glandlike structure formed, known as corpus luteum (CL)
- CL secretes estrogen, progesterone, inhibin
- If the discharged egg (now in a fallopian tube) is not fertilized, CL reaches its maximum development within ± 10 days.
- CL then rapidly degenerates by apoptosis
- It leads to menstruation and beginning of a new menstrual cycle

# Granulosa Cell

- Primordial follicles surrounded by a single layer of granulosa cells
- Granulosa cells secrete:
  - estrogen ,
  - small amounts of progesterone just before ovulation
  - peptide hormone inhibin
- During childhood granulosa cells secrete:
  - nourishment for ova
  - maturation inhibiting factor

# Granulosa Cell…..

- Further development from primordial follicle stage is characterized by
  - an increase in size of oocyte
  - a proliferation of granulosa cells into multiple layers
  - separation of oocyte from inner granulosa cells by a thick of material: zona pellucida
- Granulosa cells produce one or more factors that act on primary oocytes to maintain them in meiotic arrest

# Granulosa Cell…..

- Inner layer of granulosa cells remains closely associated with oocyte by means of cytoplasmic processes that traverse zona pellucida and form gap junctions with oocyte
- Nutrients and chemical messengers are passed to oocyte through gap junctions
- Granulosa cells produce one or more factors that act on primary oocytes to maintain them in meiotic arrest

# Theca Formation

- As follicle grows by mitosis of granulosa cells, connective tissue cells surrounding granulosa cells differentiate and form layers known as theca
- Shortly after theca formation,
  - Primary oocyte reaches full size (115 μm in diameter)
  - Antrum (fluid-filled space) begins to for in the midst of granulosa cells as result of fluid they secrete

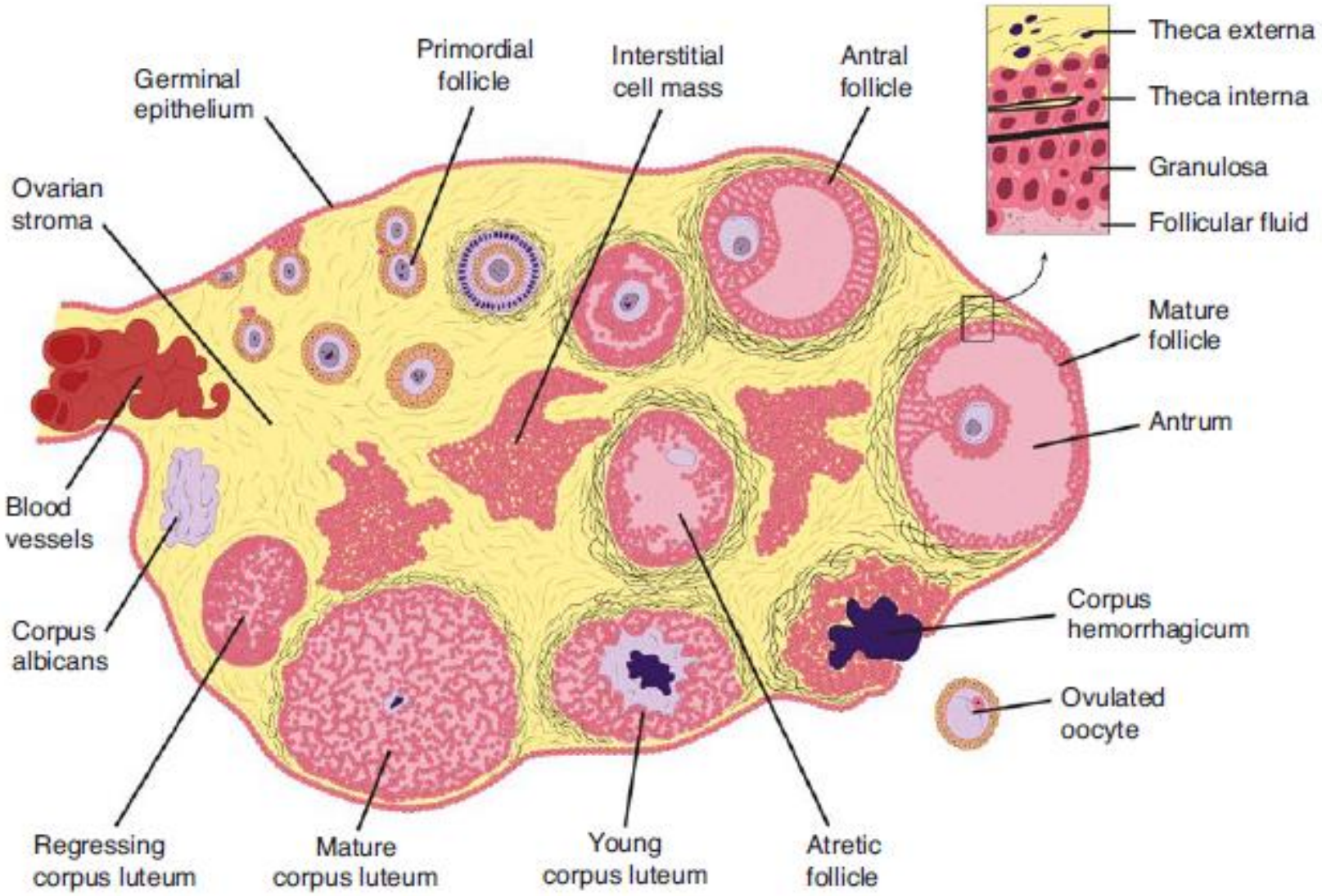



**Illustration of an ovary shows sequential development of follicle, the formation of corpus luteum and follicular atresia**

# Process of Atresia

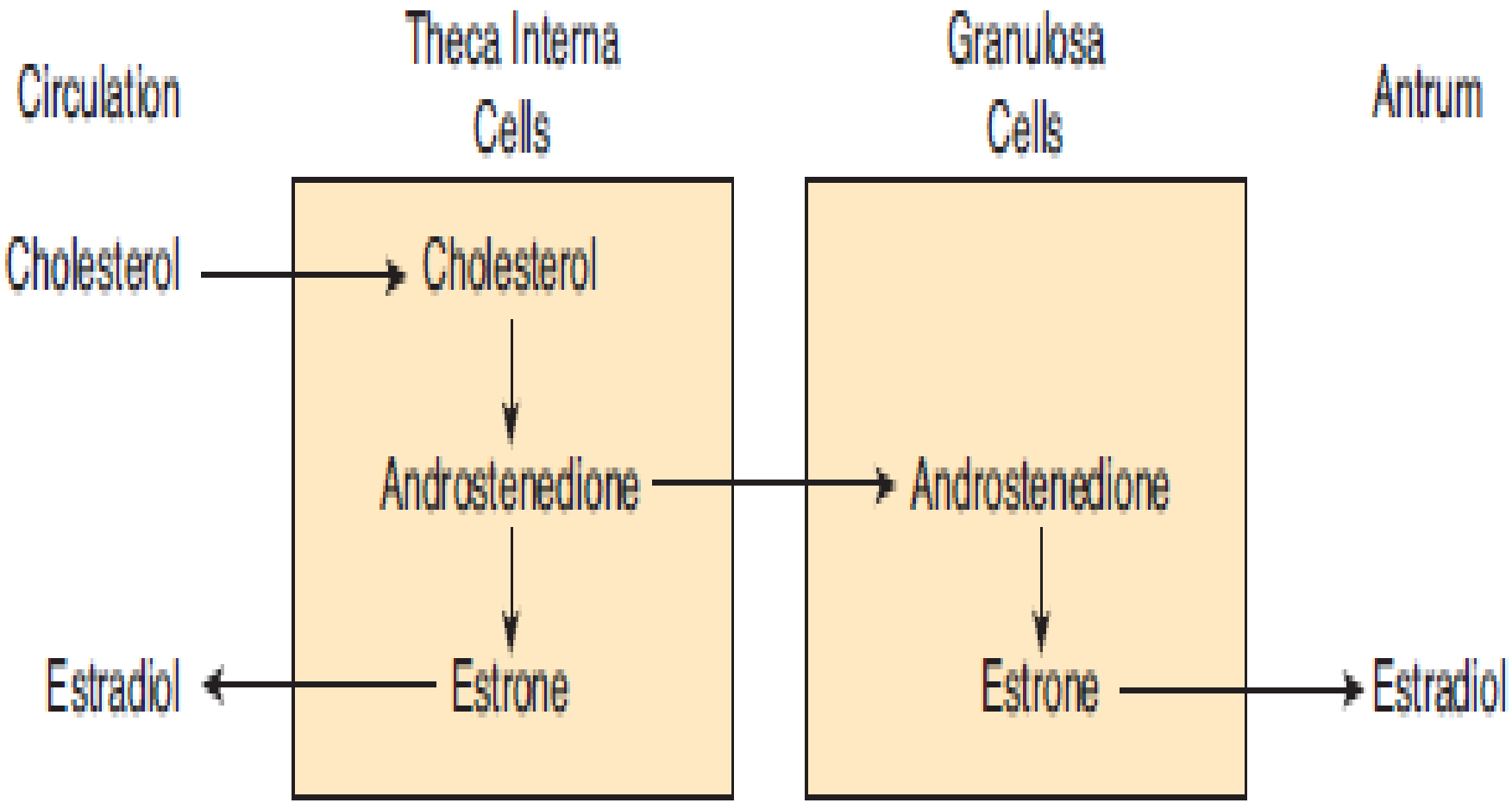
- Atresia is not limited to just antral follicles, follicles can undergo atresia at any stage
- This process is already occurring in utero so that the 2-4 million follicles and eggs are present at birth represent only a small fraction of those present at earlier time in the fetus
- Atresia then continues all through pubertal life so that only 200,000-400,000 follicles remain when active reproductive life begins.
- Atresia still continues during reproductive life

# Process of Atresia…..

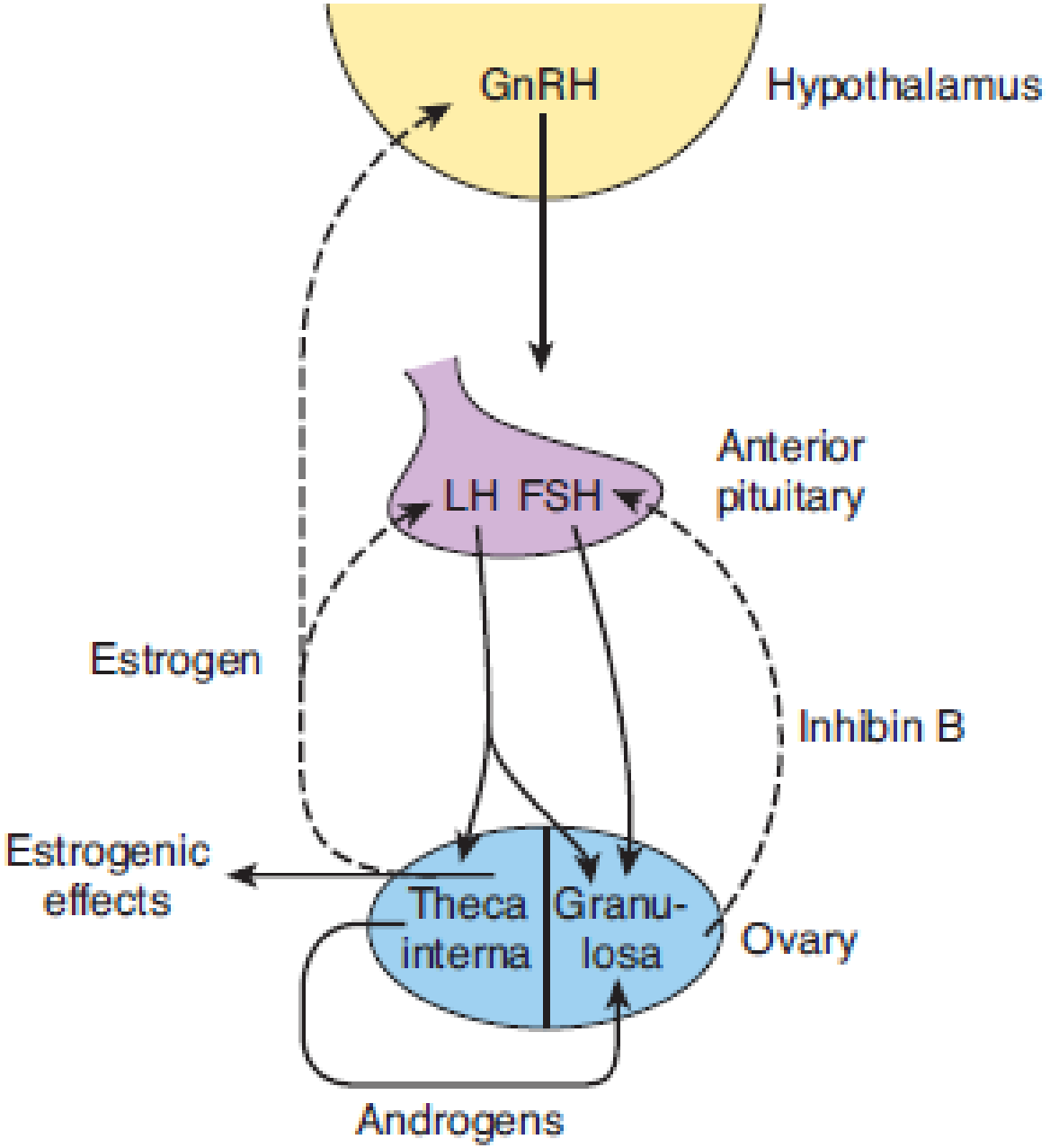
- **Therefore, 99,99 % of ovarian follicles present at birth will undergo atresia**

# Sites of Synthesis of Ovarian Hormone

- **Estrogen is synthesized and released into blood:**
  - **during follicular phase mainly by granulosa cells**
  - **after ovulation, by CL**
- **Progesterone is synthesized and released into blood:**
  - **in very small amounts by granulosa and theca cells just before ovulation**
  - **major source is CL (after ovulation)**
- **Inhibin is synthesized and released into blood:**
  - **by granulosa cells**
  - **CL**




**Interactions between theca and granulosa cells in estradiol synthesis and secretion**




**Feedback regulation of ovarian function.**

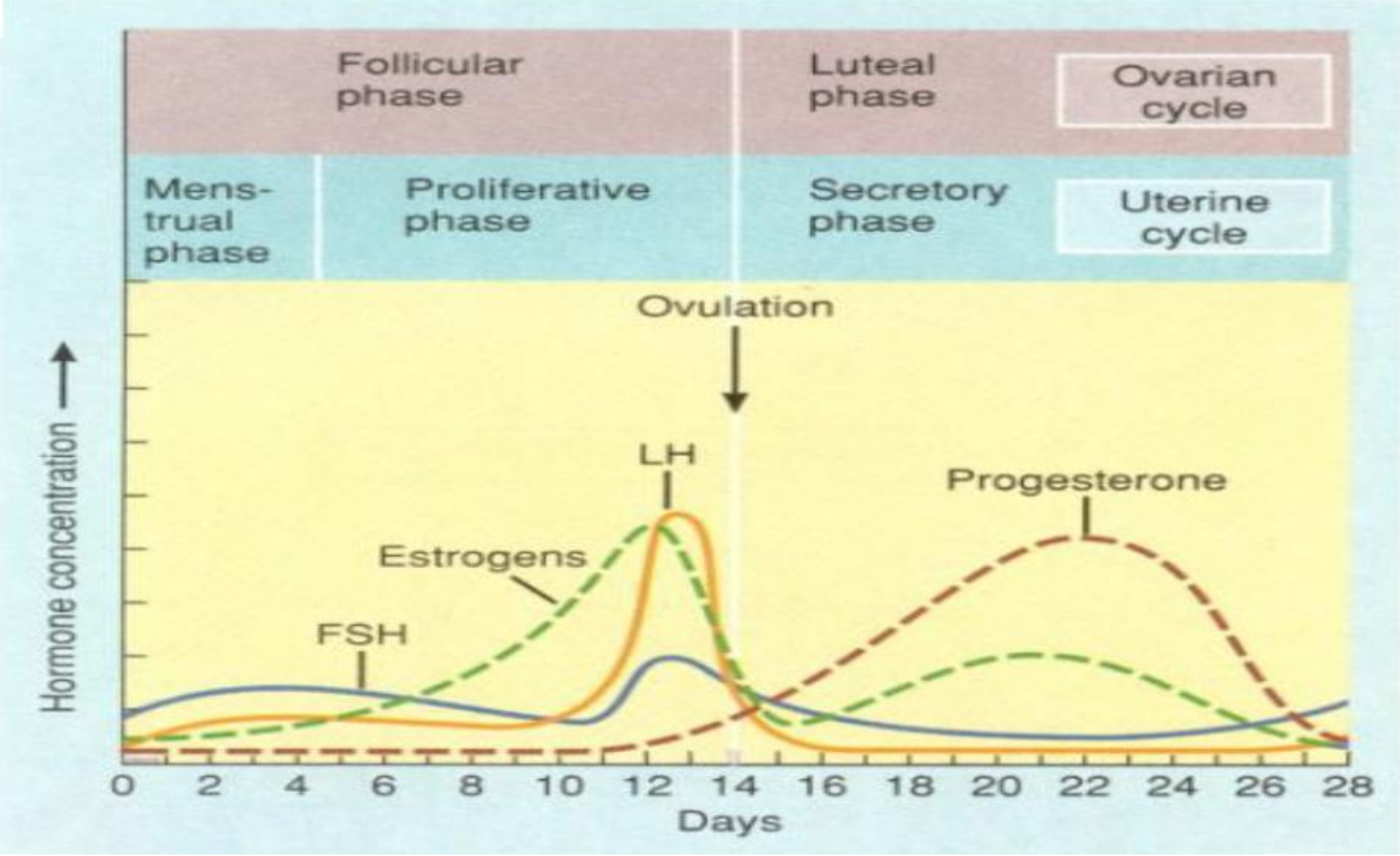
# Ovarian Cycle

1. **The follicular phase:**
   - **ovarian follicle growth**
   - **ovulation**

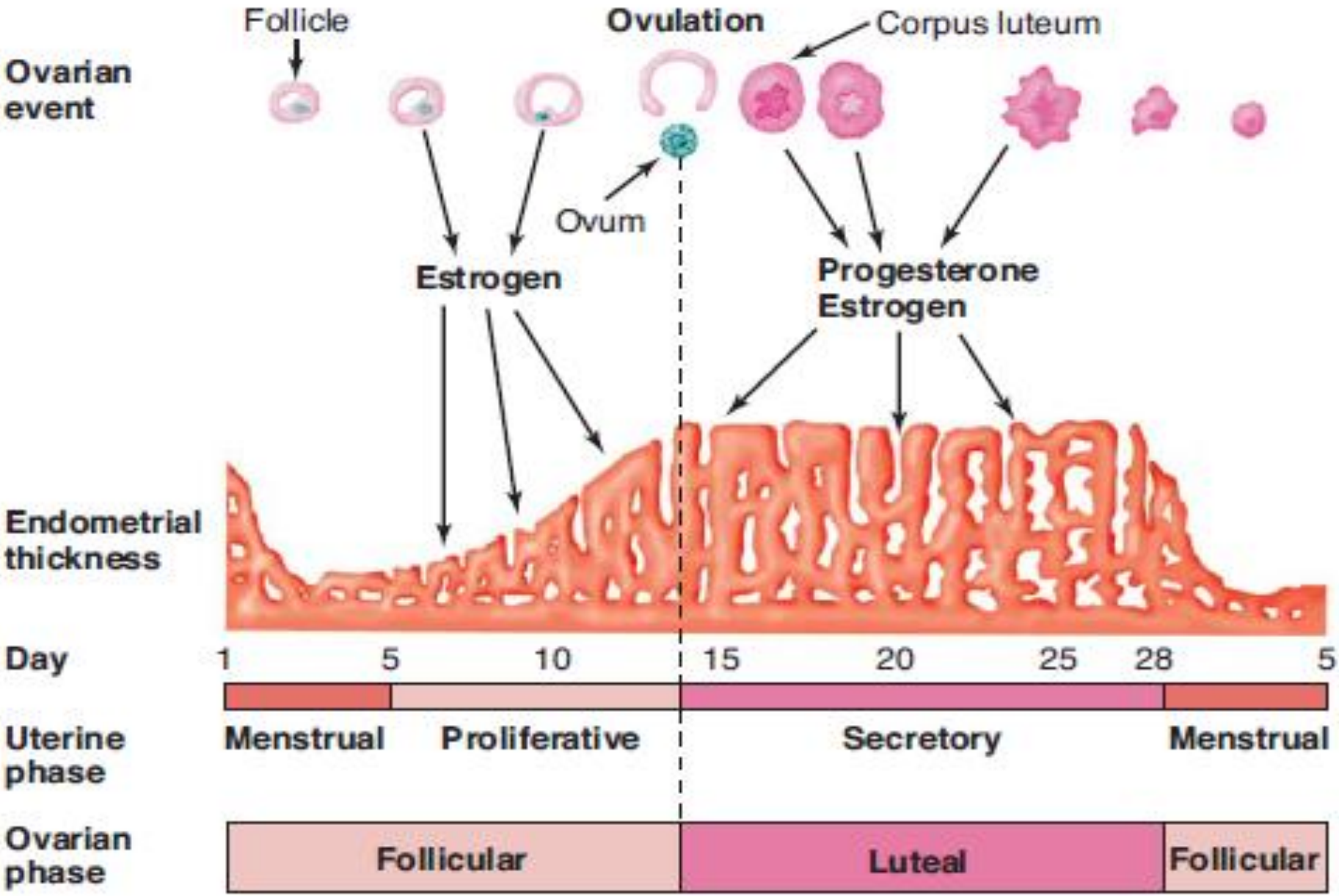
2. **The luteal phase:**
   - **development of corpus luteum**

# Uterine Cycle

1. **Proliferative phase:**
   - estrogen → estrogen phase
   - before ovulation
2. **Secretory phase:**
   - progesterone → progestational phase
   - after ovulation
3. **Menstruation**
   - estrogen & progesterone decreased




**Relative concentrations of anterior pituitary gland hormones (FSH – LH) and ovarian Hormones (estrogen – progesterone) during a normal female sexual cycle. Note the relationship of the hormones to the ovarian and uterine cycles**

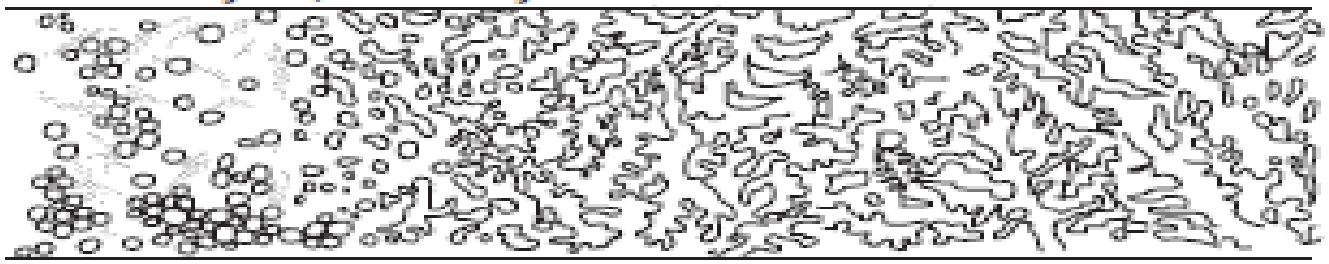



Relationship between ovarian and uterine changes during the menstrual cycle.

# Cyclical Changes in Cervix

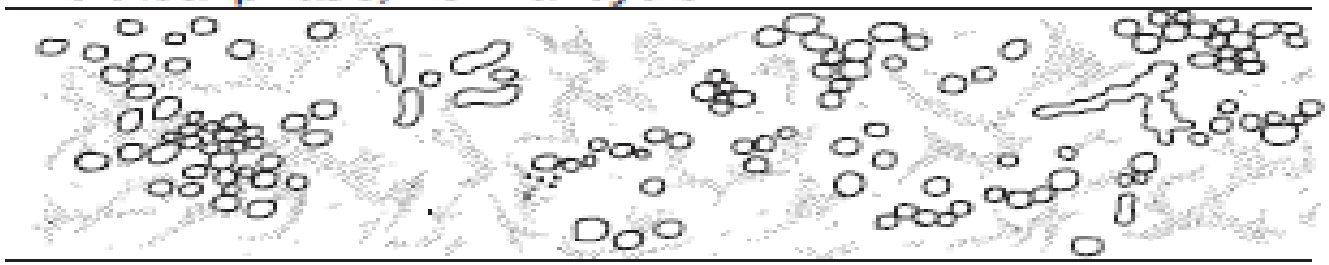
- The mucosa of cervix does not undergo cyclical desquamation
- There are regular changes in cervical mucus:
  - Estrogen makes the mucus thinner, watery, and more alkaline → promotes the survival and transport of sperms
  - At the time of ovulation the mucus is:
    > thinnest and fern-like pattern on slide
    > its elasticity increases → a drop can be stretched into a long (8 - ≥12cm), and thin thread
  - Progesterone makes the mucus thick, tenacious, and cellular
  - After ovulation and during pregnancy: thick, no fern-pattern

Normal cycle, 14th day



**Estrogen:**
**fern-like pattern**

Midluteal phase, normal cycle



**Progesterone:**
**no fern-like pattern**

Anovulatory cycle with estrogen present

**Estrogen,**
**no progesterone:**
**Fern-like pattern**

**Microscopic of patterns formed of cervical mucus on dried smeared slide.**
**Progesterone makes the mucus thick and cellular.**
**In anovulatory, no progesterone is present to inhibit fern-like pattern**

# Cyclical Changes in Vagina

- **Under influence of estrogen:**
  - **the vaginal epithelium becomes cornified that can be identified in the vaginal smear**
- **Under influence of progesterone:**
  - **secretion of thick mucus**
  - **the vaginal epithelium proliferates and becomes infiltrated with leukocytes**
- **The cyclical changes in vaginal smear in rats are relatively marked; in humans and other species are similar, but not so clear cut**

# Cyclical Changes in Breast

- Although lactation normally does not occur until the end of pregnancy, cyclical changes take place in the breasts during the menstrual cycle
- Estrogens cause proliferation of mammary ducts
- Progesterone causes: growth of lobules and alveoli
- The breast swelling, tenderness, and pain experienced by many women during the 10 day preceding menstruation ← due to distention of the ducts, hyperemia, and edema of the breast interstitial tissue
- All the changes regress along with symptoms, during menstruation

# Normal Menstruation

- Menstrual blood is predominantly arterial, only 25% of the blood being of venous origin
- Containing tissue debris, prostaglandins, and relatively large amount of fibrinolysin from endometrial tissue
- Fibrinolysin lyses clots → no clots in menstrual blood
- Usual duration is 3-5 d, but 1-8 d can occur normally
- The average amount of blood lost is 30 ml (range normally from light spotting – 80 ml)
- The amount of blood affected by various factors, including the thickness of endometrium, medication, and diseases that affect clotting mechanism

# Anovulatory Cycles

- Anovulatory cycles are common for the first 12-18 months after menarche and before the onset of menopause
- When ovulation does not occur → no CL → effects of progesterone on endometrium are absent
- Estrogens continue to cause growth, and proliferative endometrium becomes thick enough to break down and begins to slough
- The time it takes for bleeding usually < 28 d from the last menstrual period
- The flow is variable from scanty to relatively profuse

# Thank You