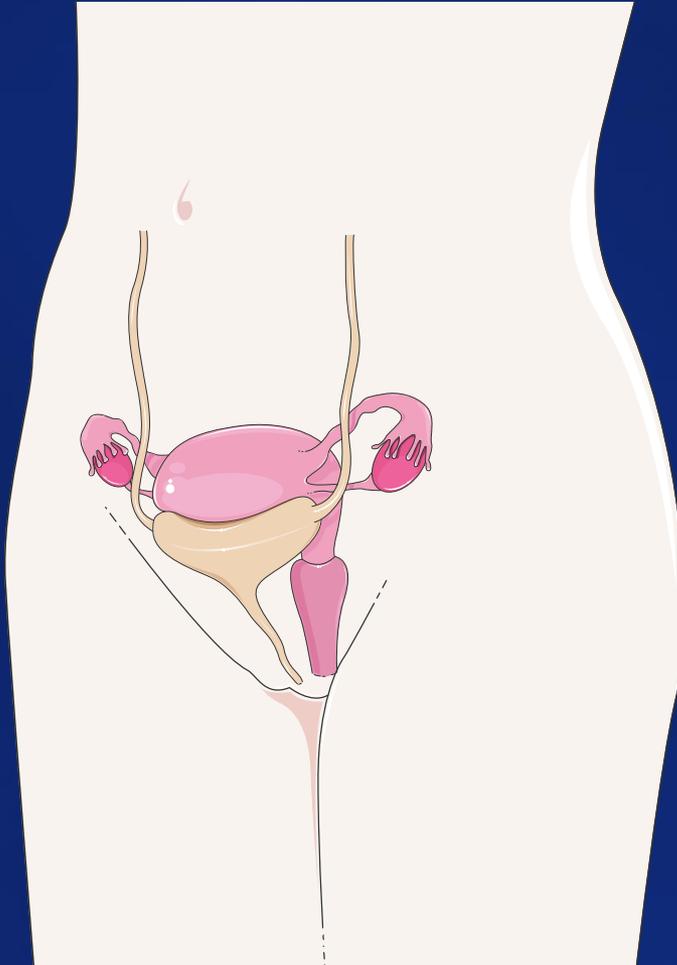
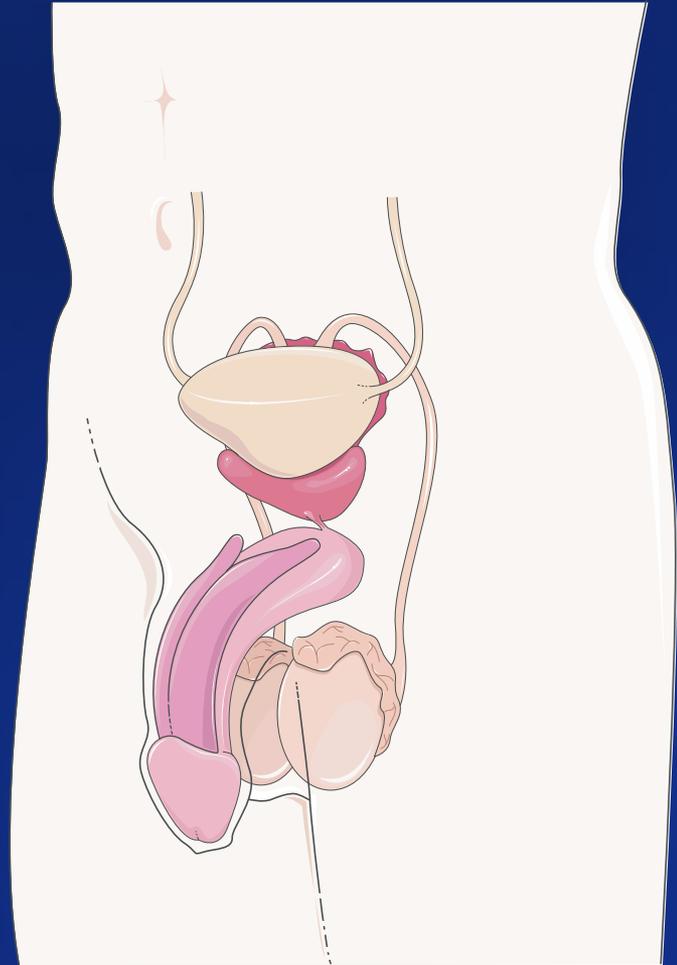


Genital apparatus



Female



Male

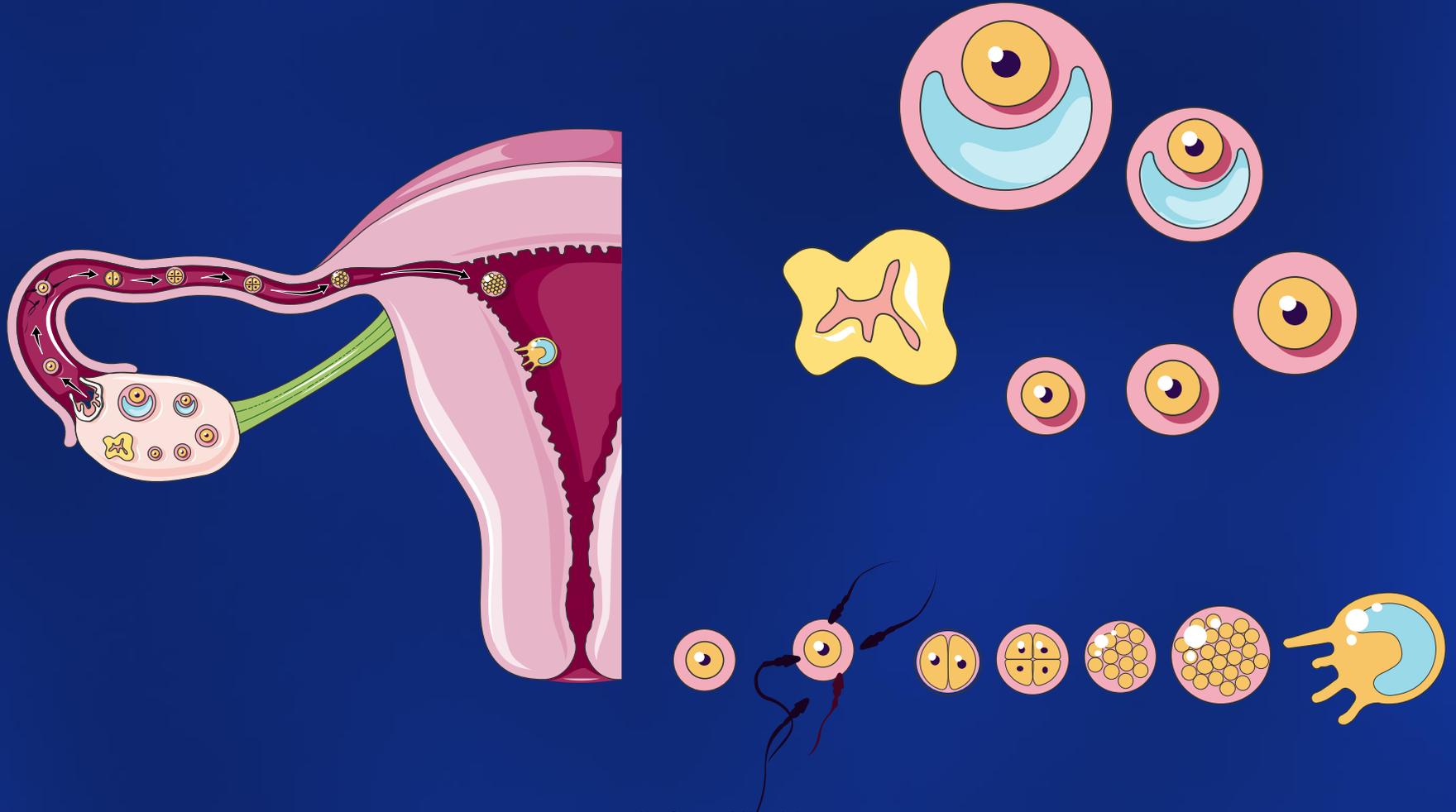
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Ovary and Ovum



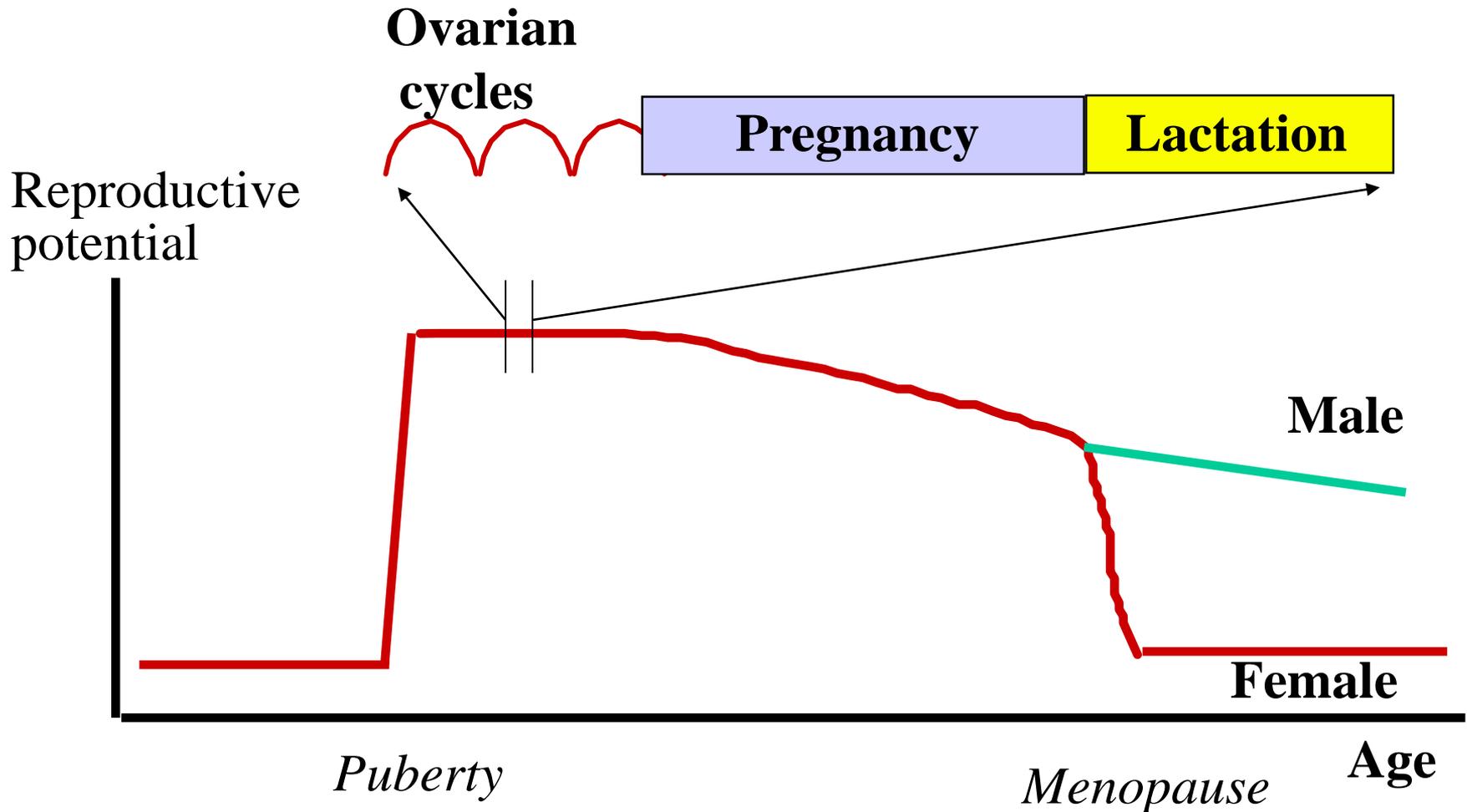
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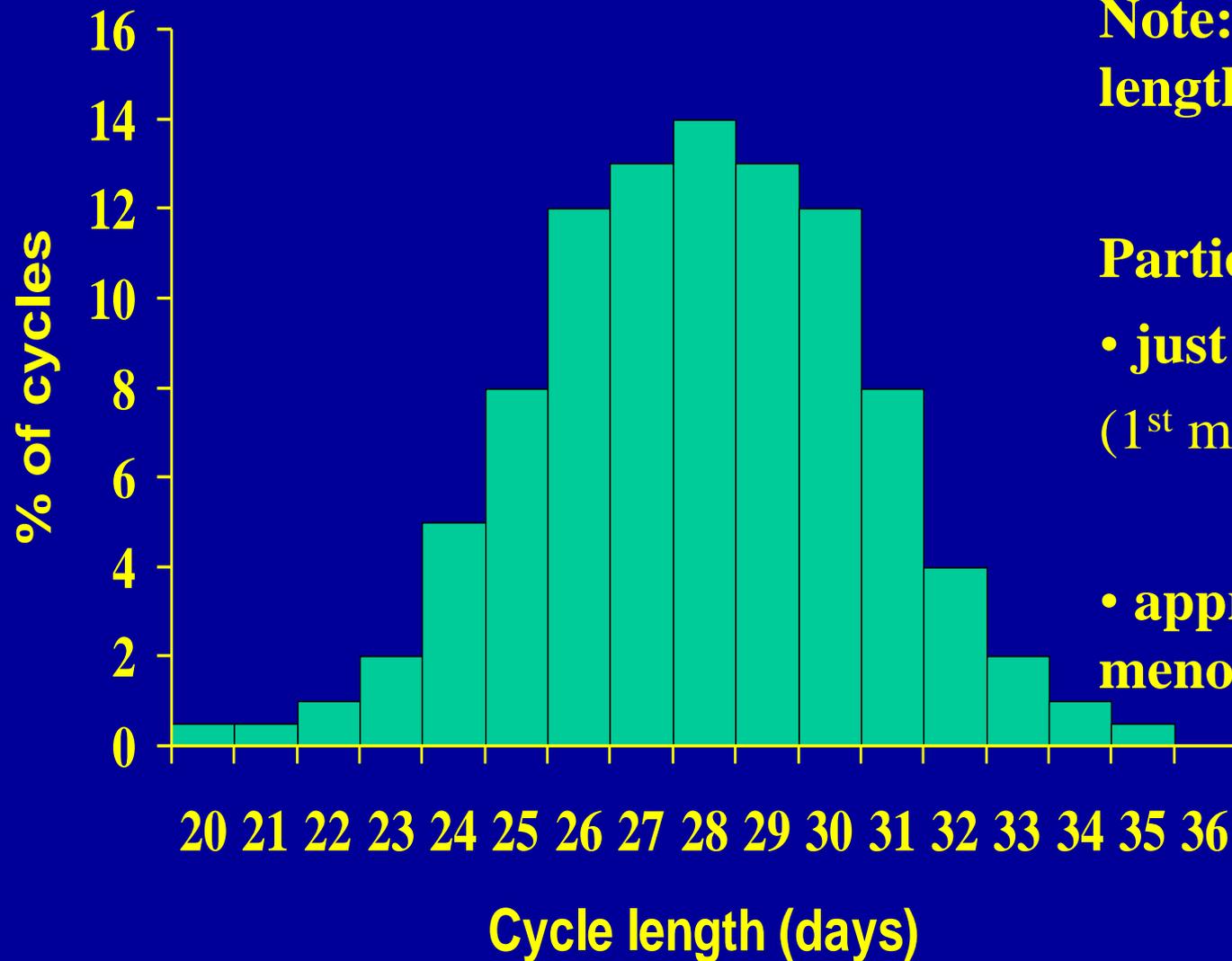
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The reproductive lifespan



Menstrual cycle lengths



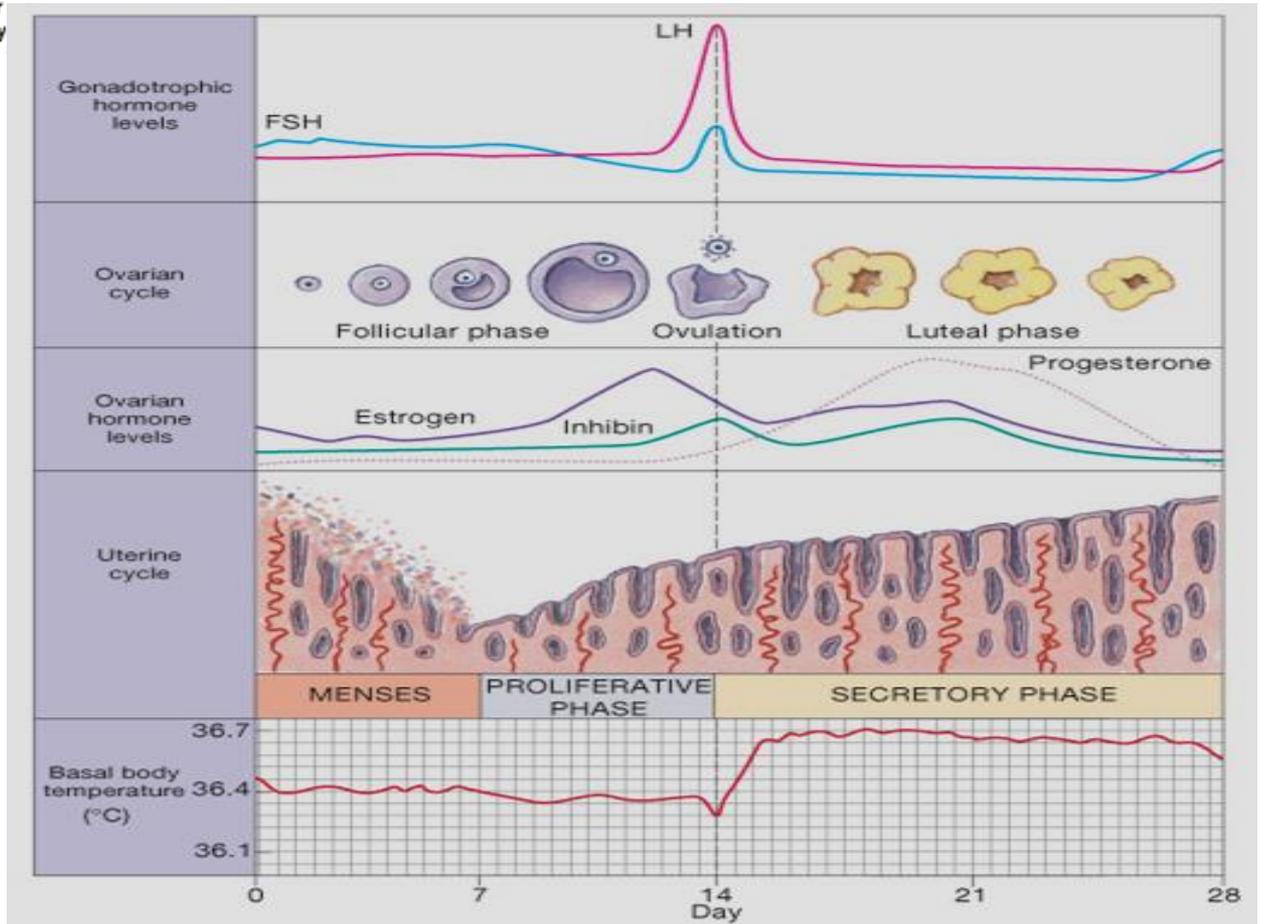
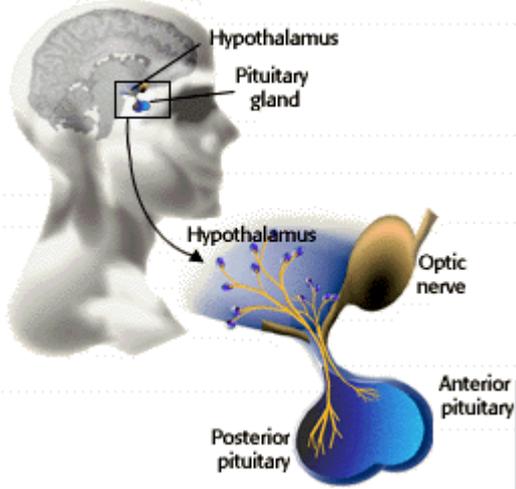
Note: Variations in cycle length are normal!

Particularly:

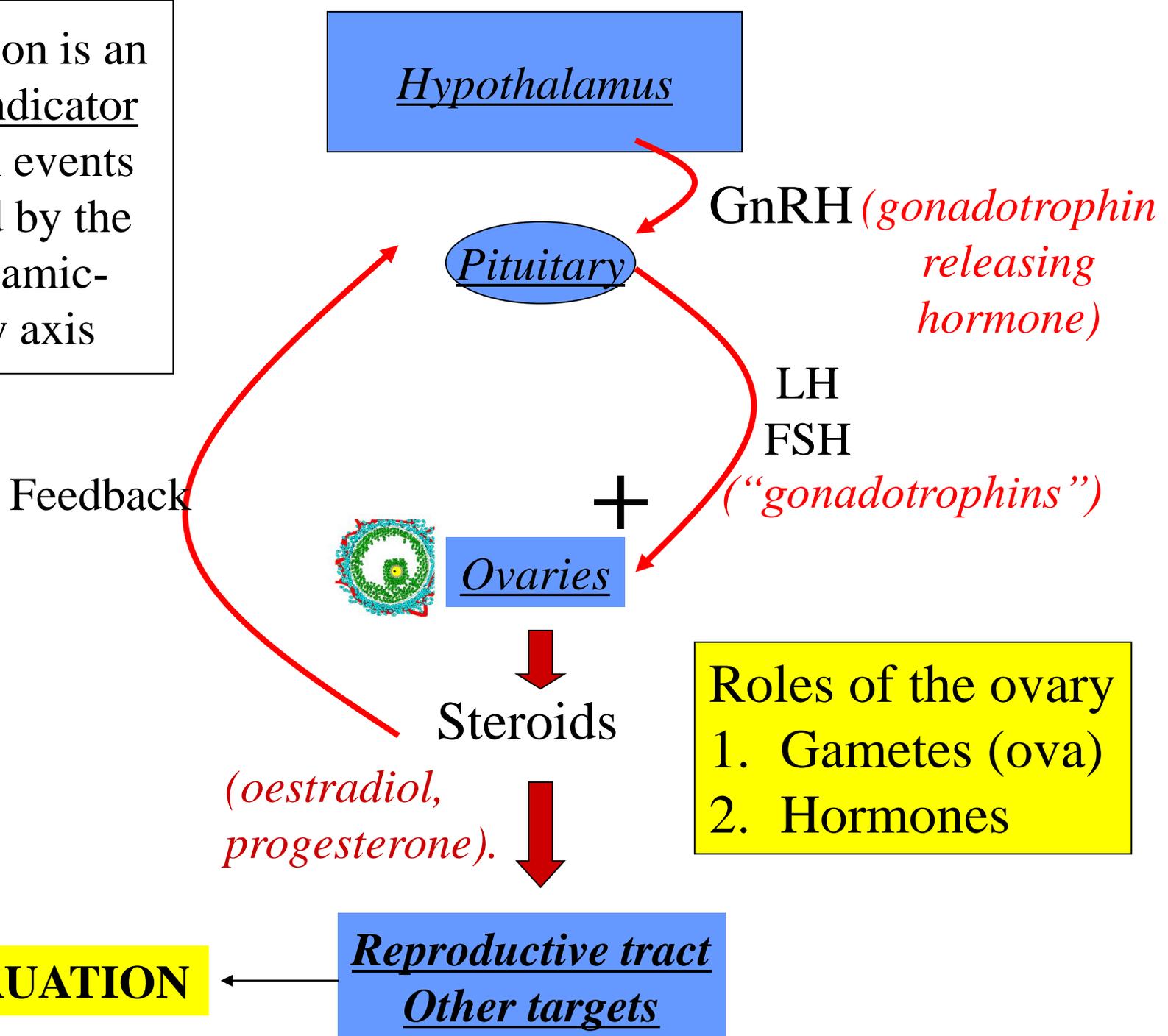
- **just after menarche**
(1st menstrual period)

- **approaching the menopause**

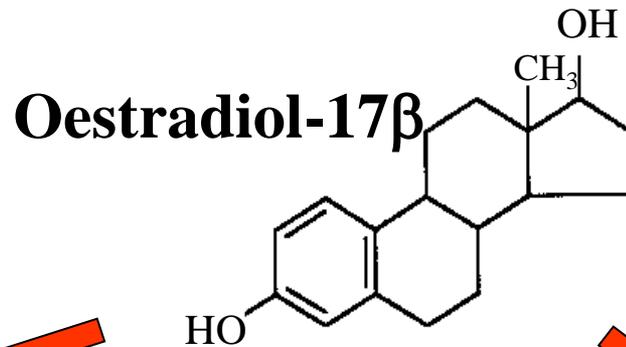
Hypothalamus & pituitary gland



Menstruation is an external indicator of ovarian events controlled by the hypothalamic-pituitary axis



What are oestrogens?



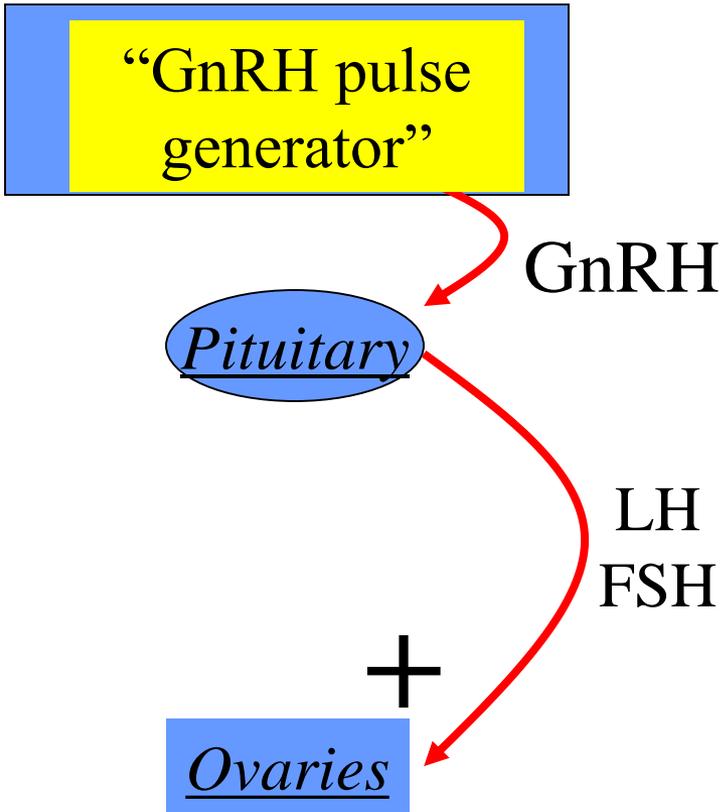
Ovaries
Testes
Placenta

Answer: Steroids with characteristic effects, esp. on female reproductive tract. Some are more potent than others.

Breast

Cardiovascular
system

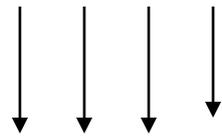
Reproductive tract



Pulsatile activity of GnRH neurones

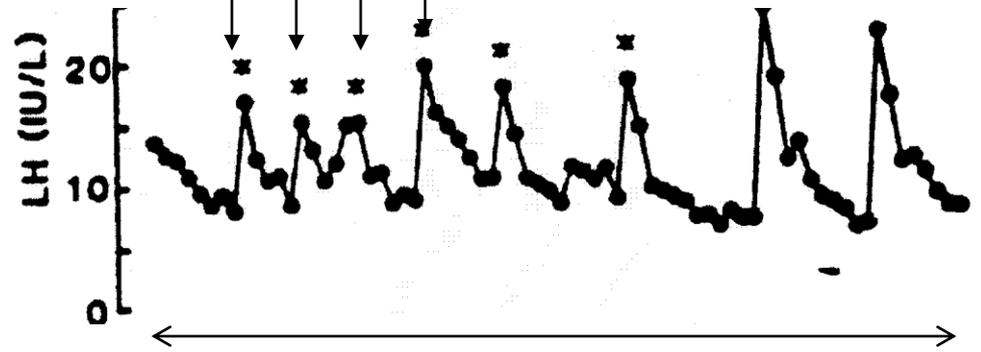


Pulses of GnRH



Pulses of LH

Plasma LH



Natural suppression

Before puberty

Lactation

Diet induced

Anorexia

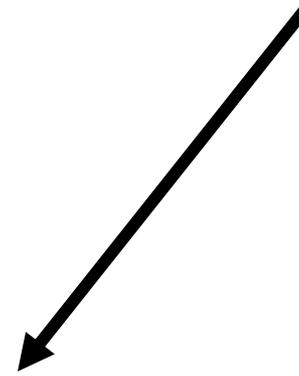
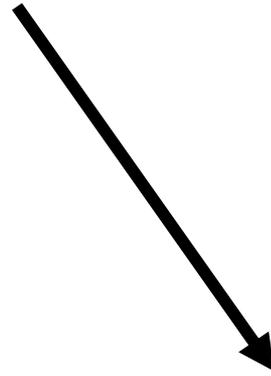
Malnutrition

Exercise

Modulation during
menstrual cycle

Diet

Stress?



Hypothalamic neurones

“GnRH pulse generator”



Frequency and amplitude
of GnRH pulses



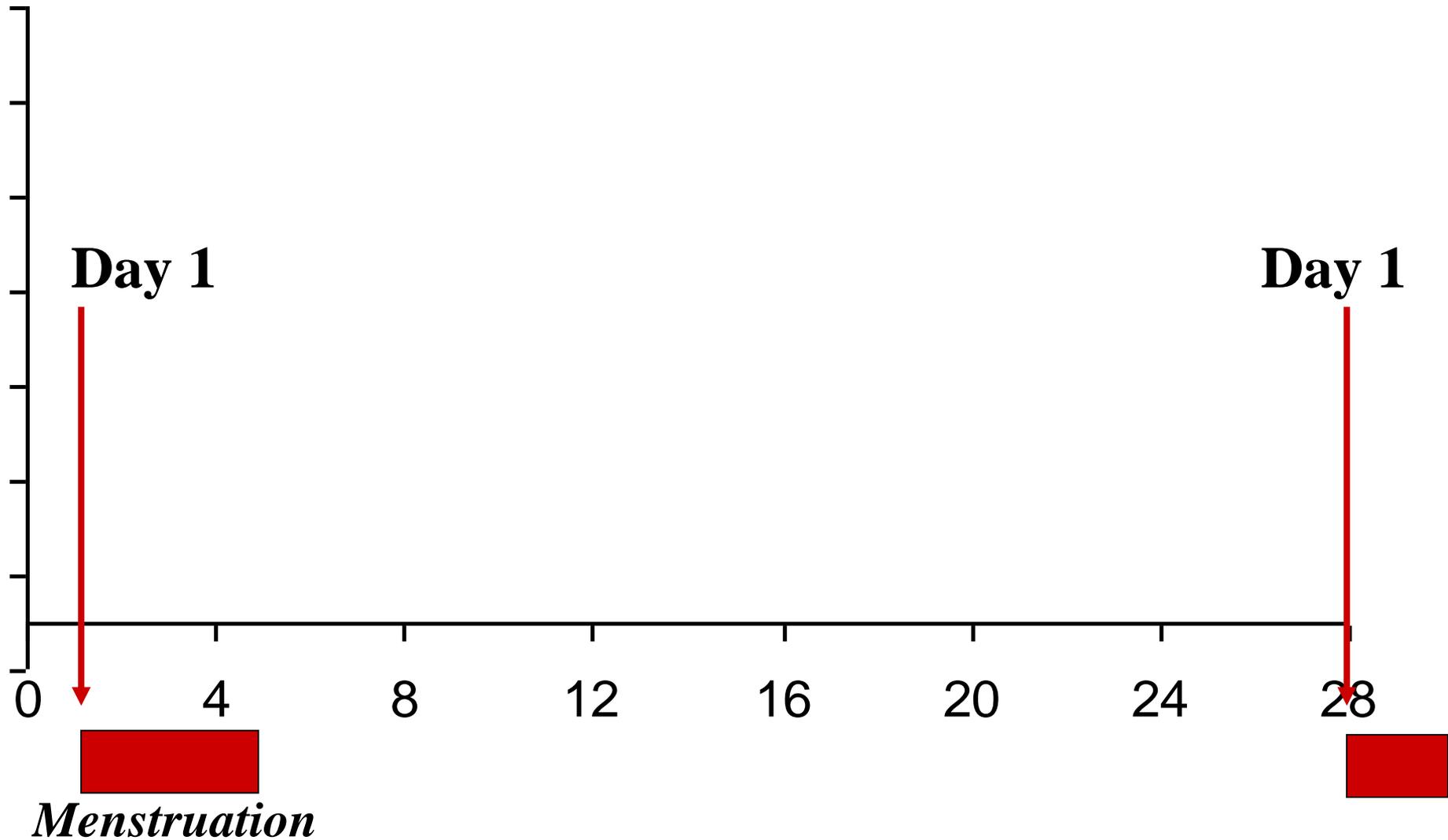
Pituitary



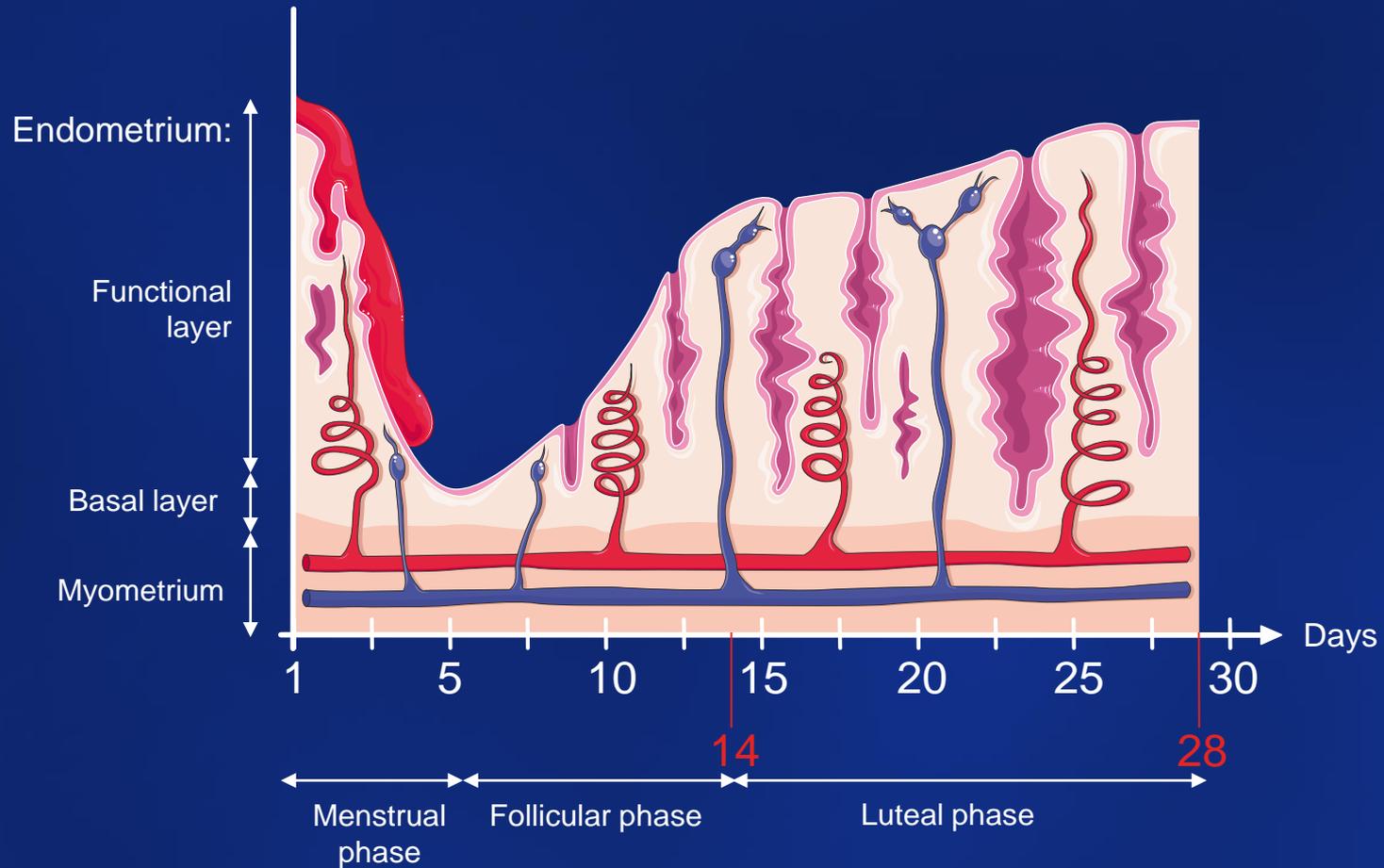
Changing patterns of
LH and FSH

Timing events in the menstrual cycle.

1. Onset of menstruation



Uterine cycle



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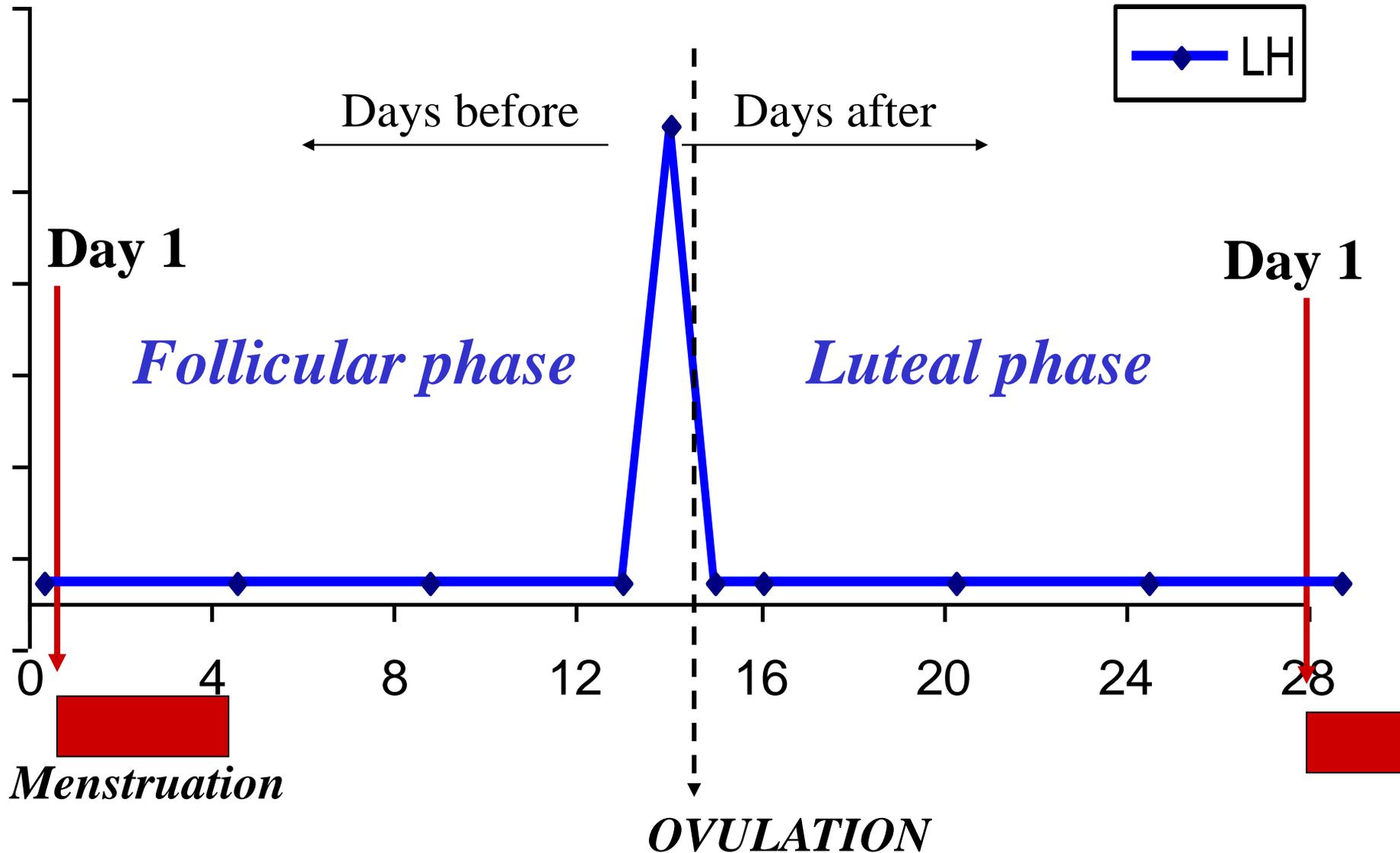
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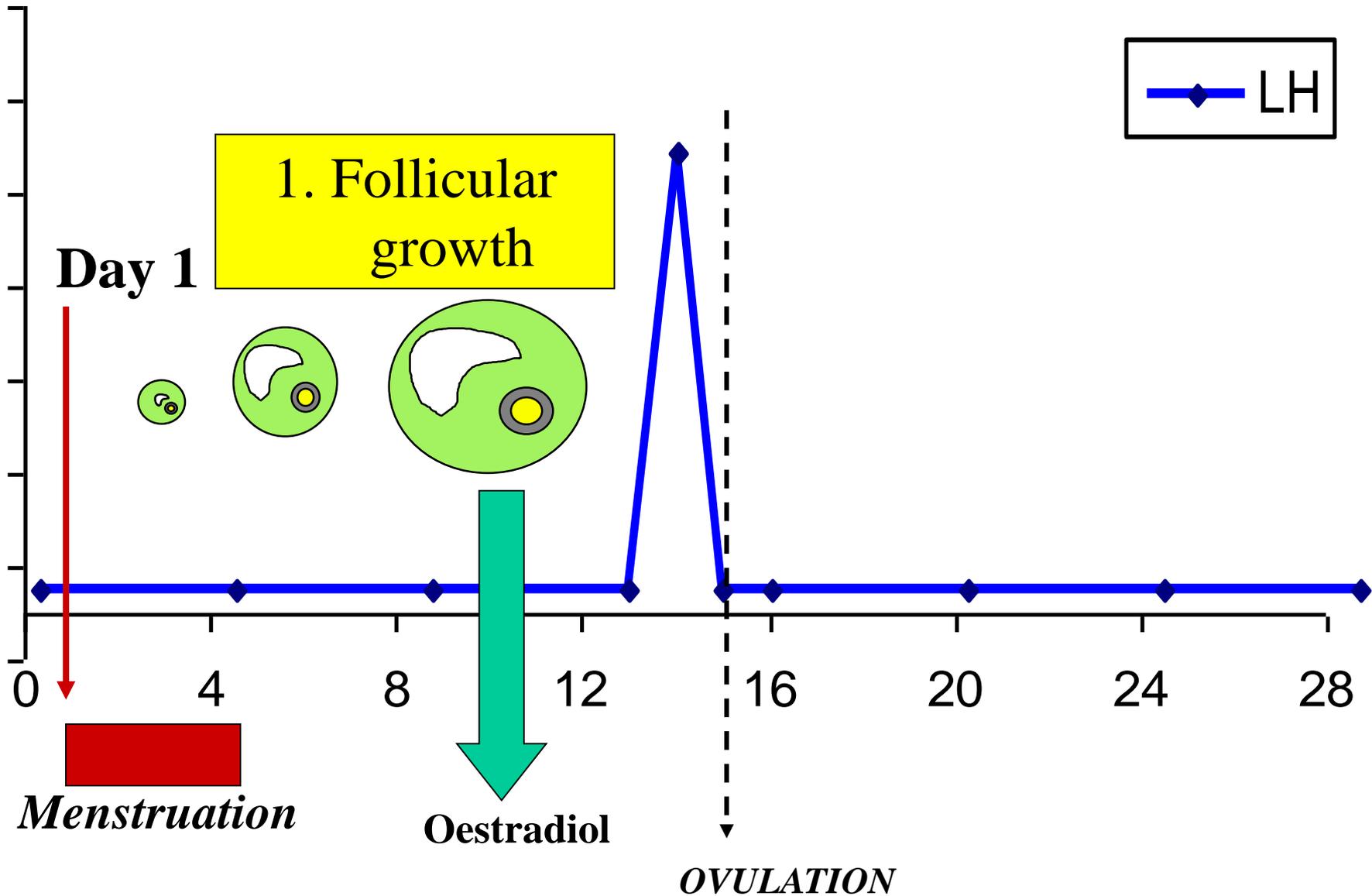
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Timing events in the menstrual cycle.

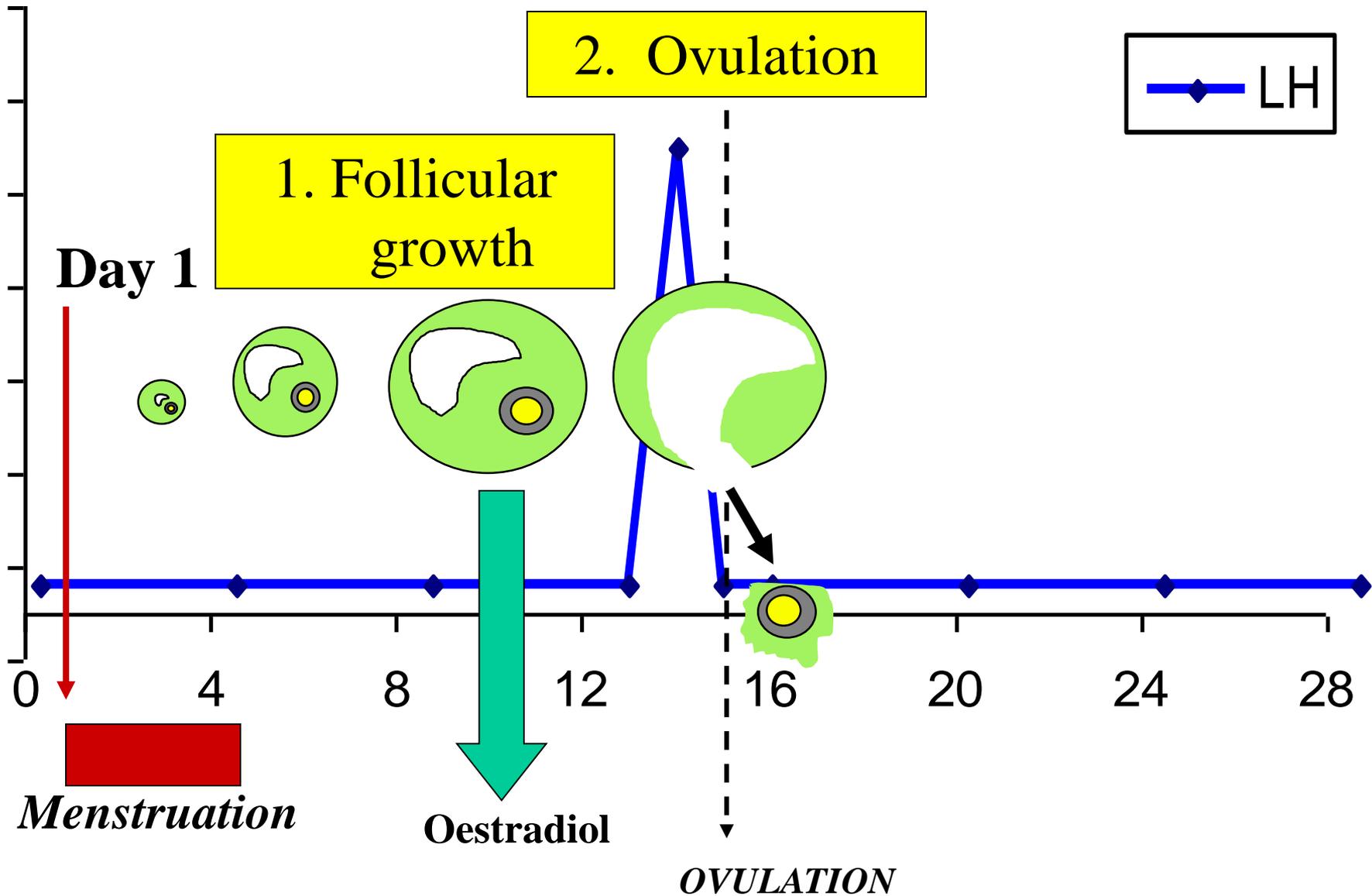
2. LH surge



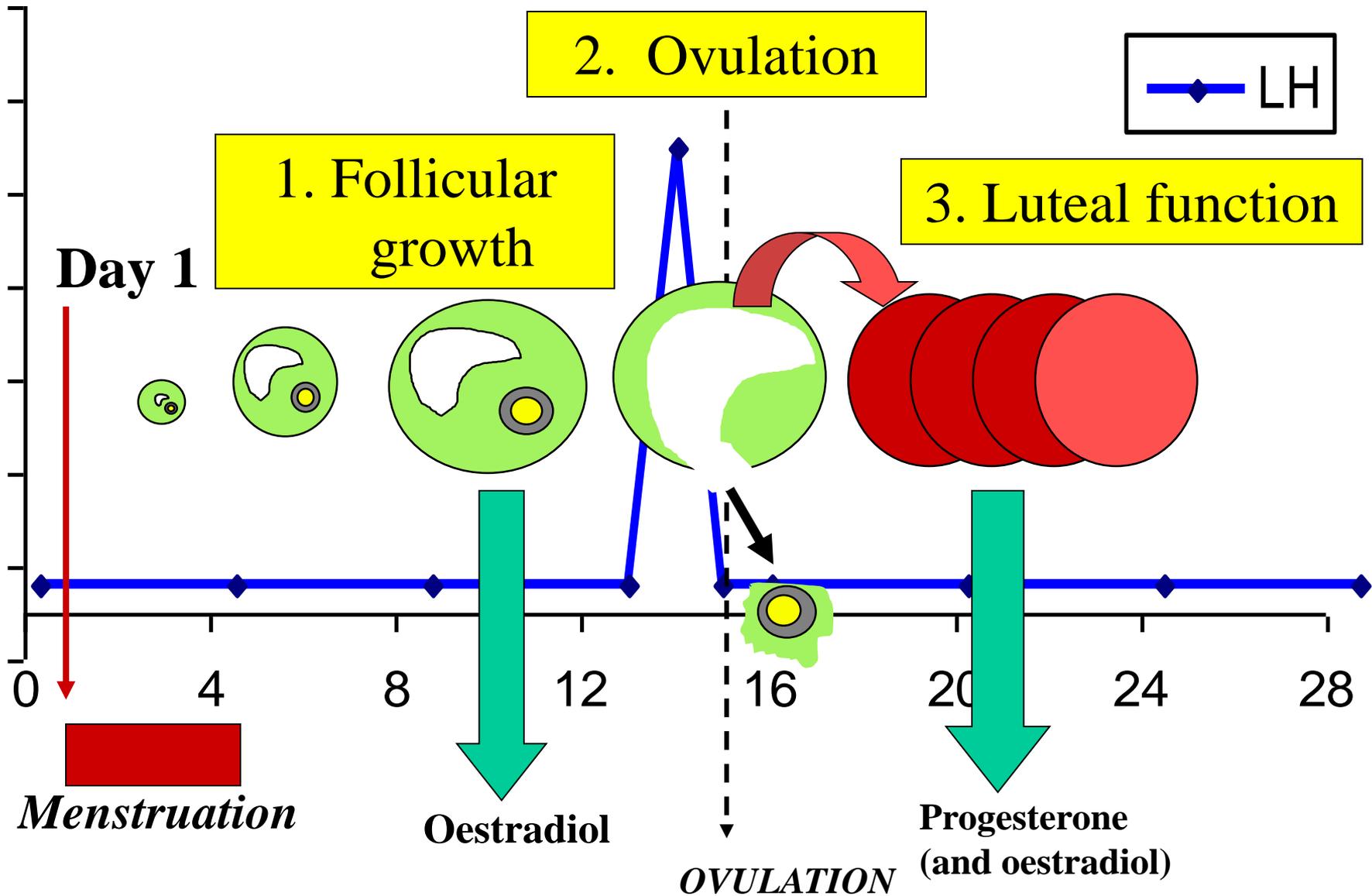
Key events in the ovarian cycle



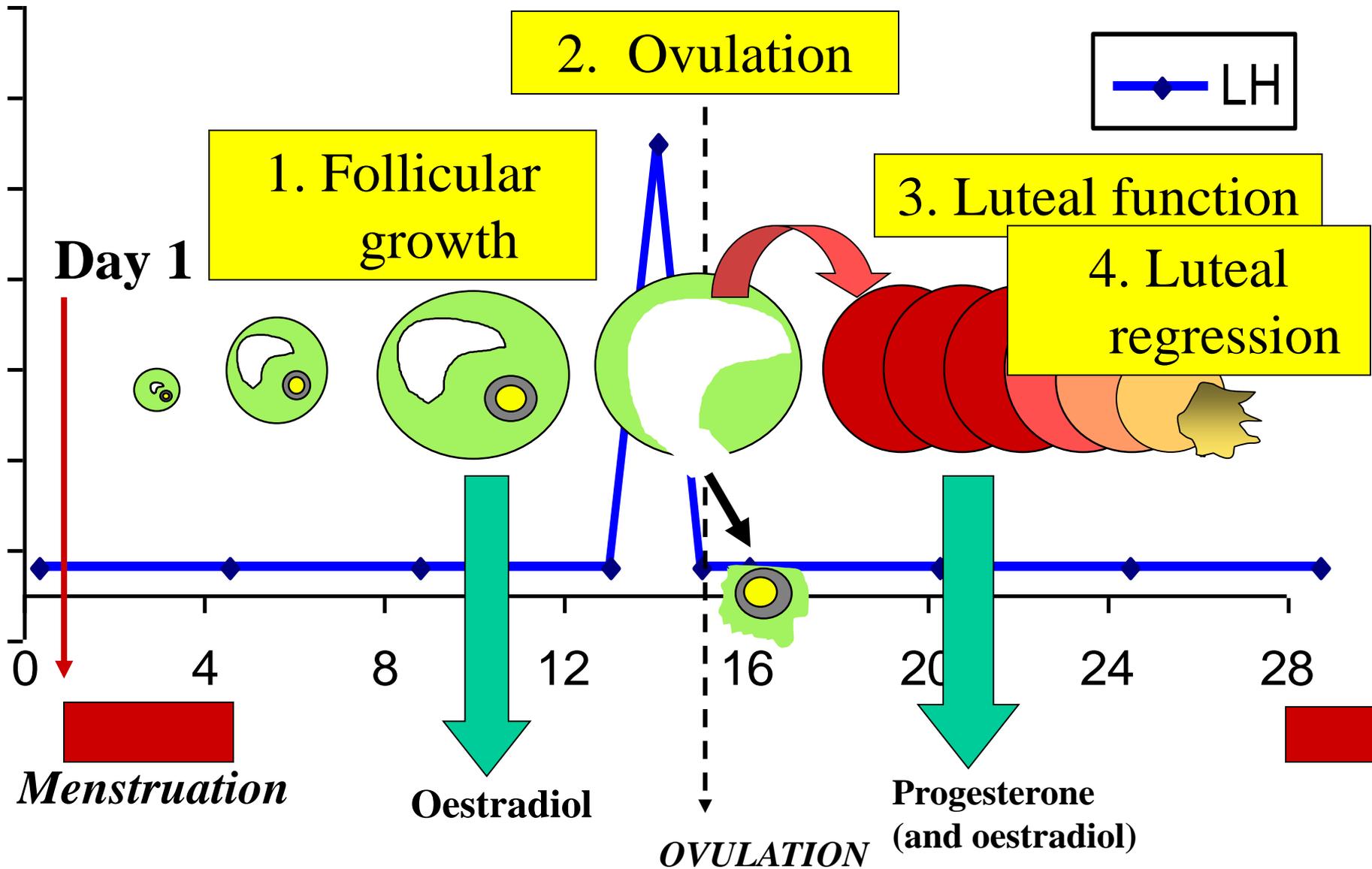
Key events in the ovarian cycle



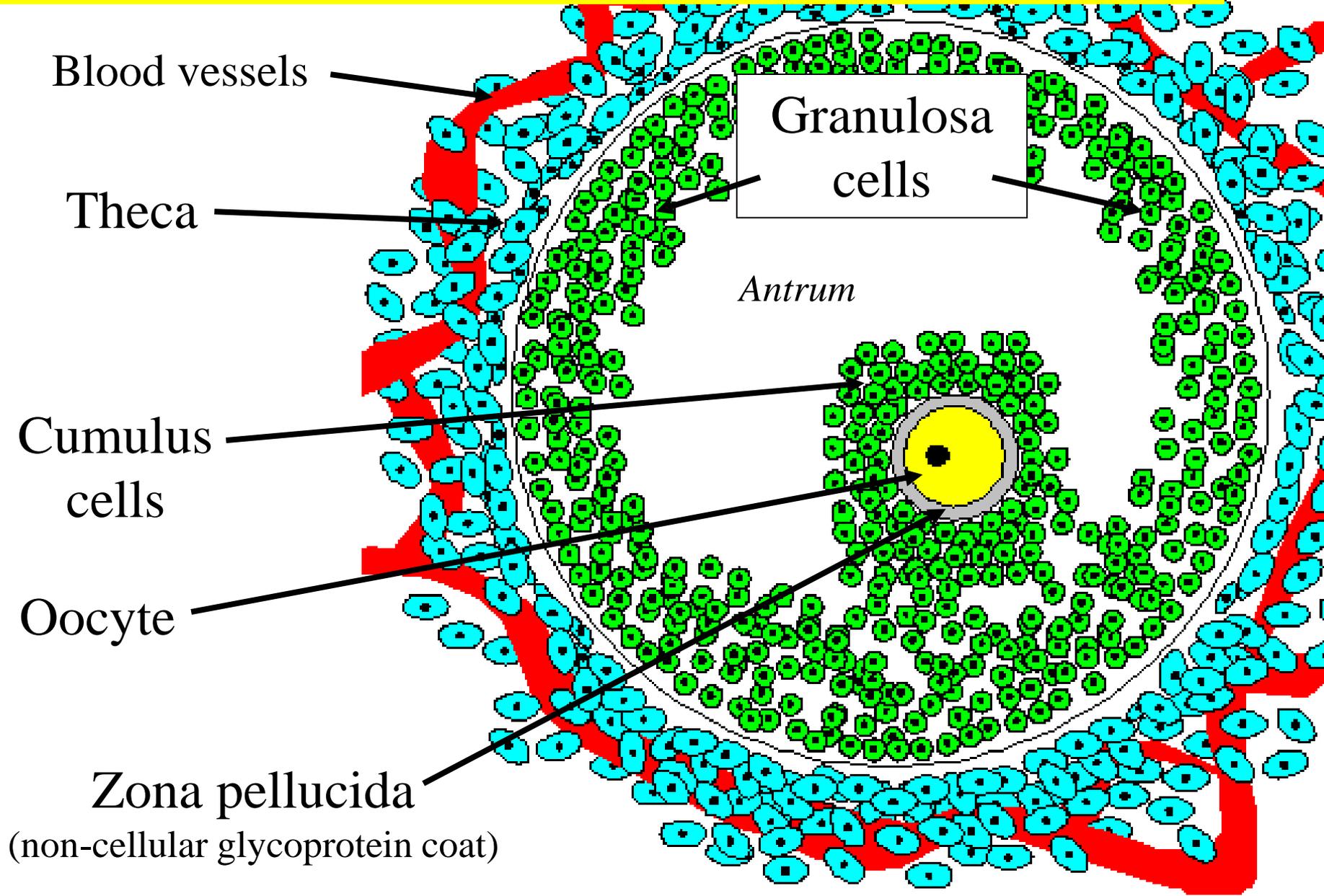
Key events in the ovarian cycle

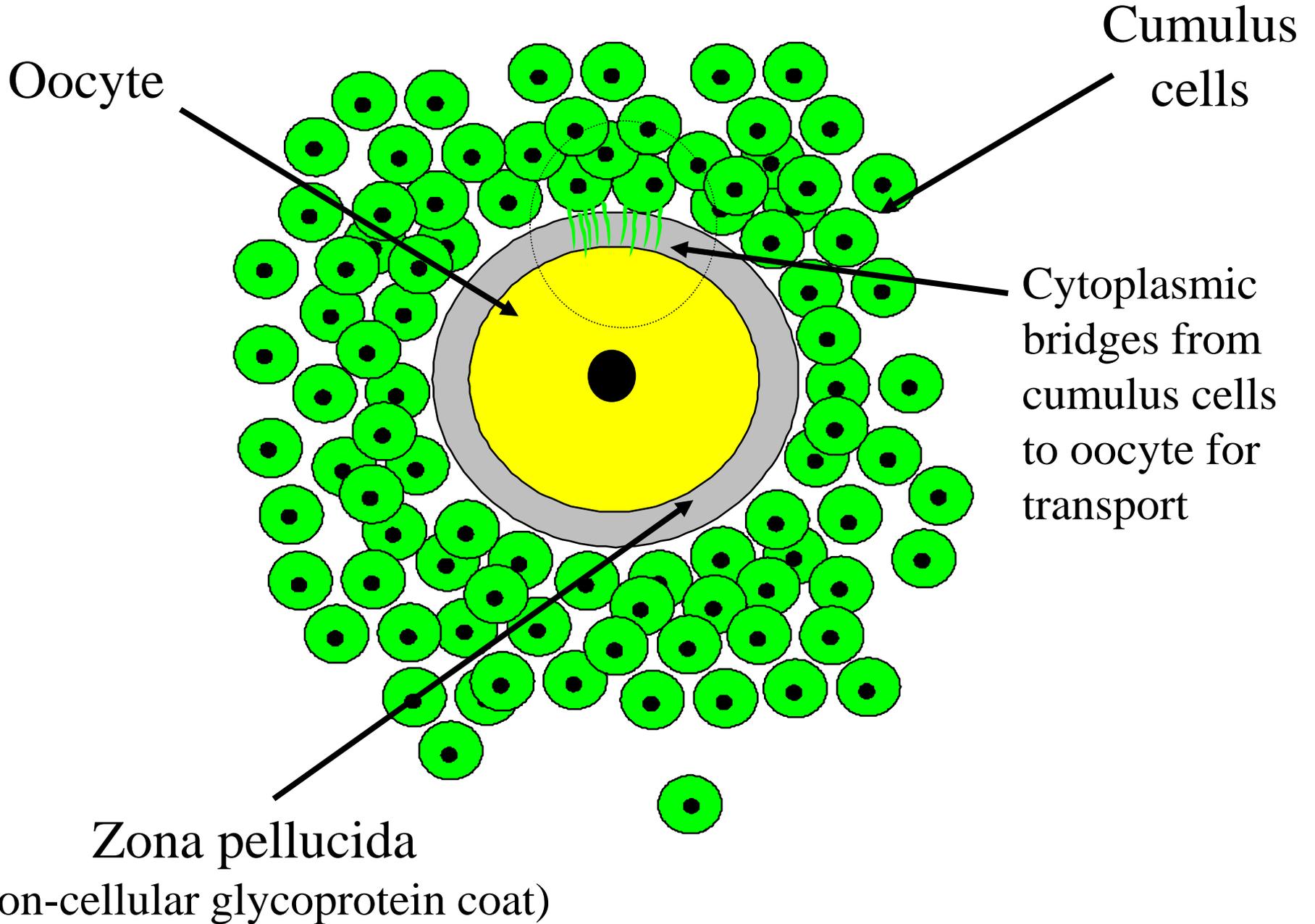


Key events in the ovarian cycle



The follicle is the fundamental element of the ovary:





Where do follicles come from?

Female

Primordial germ cells
(oogonia)



Mitoses stop
in fetal life

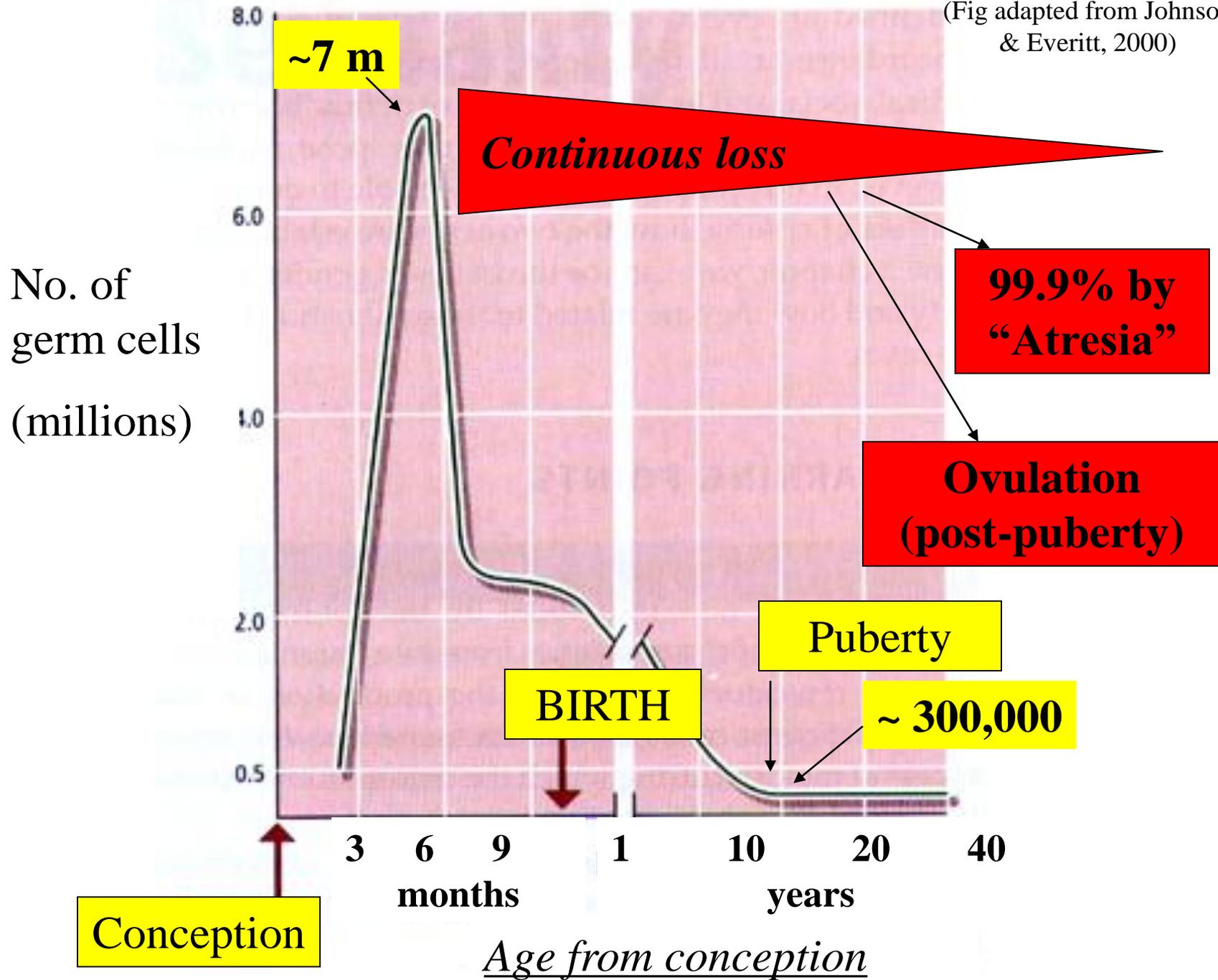


All enter
MEIOSIS

Arrested in *1st meiotic division*
“*Primary oocytes*” in
primordial follicles

This means there is
a fixed, limited pool
of oocytes.

(Fig adapted from Johnson & Everitt, 2000)



No. of germ cells (millions)

~7 m

Continuous loss

99.9% by "Atresia"

Ovulation (post-puberty)

Puberty

BIRTH

~ 300,000

Conception

months

years

Age from conception

Nuclear and cytoplasmatic maturation

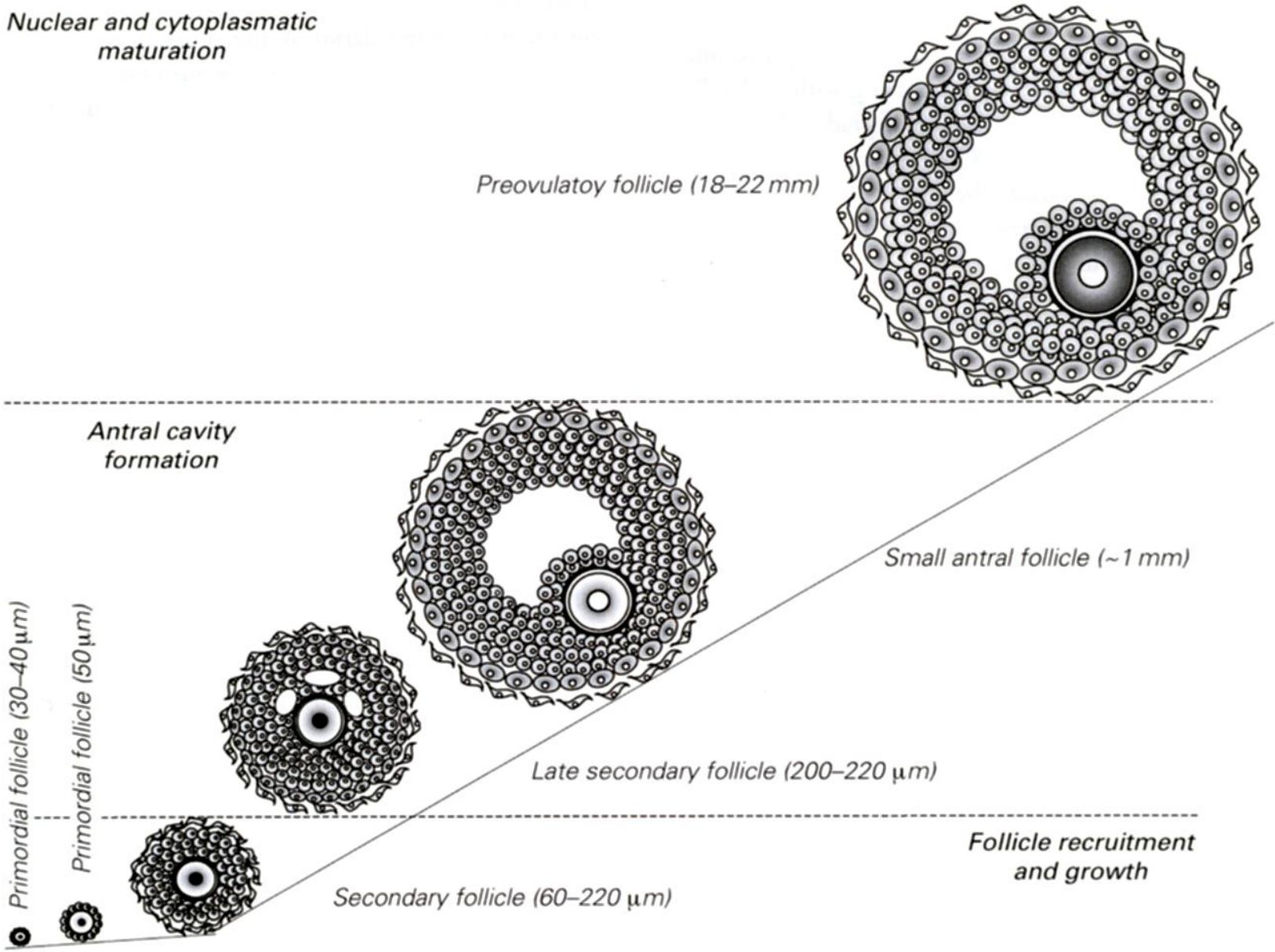
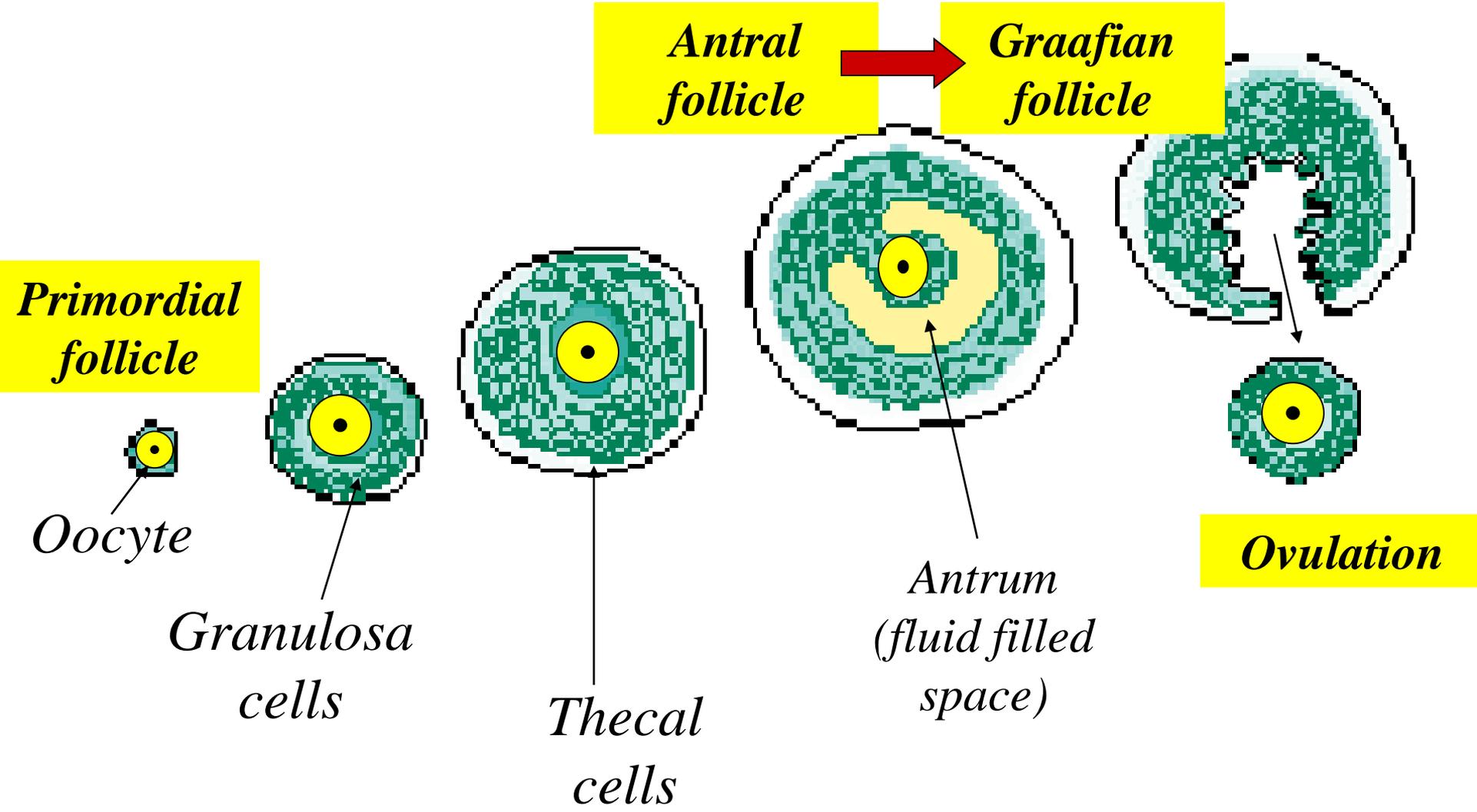


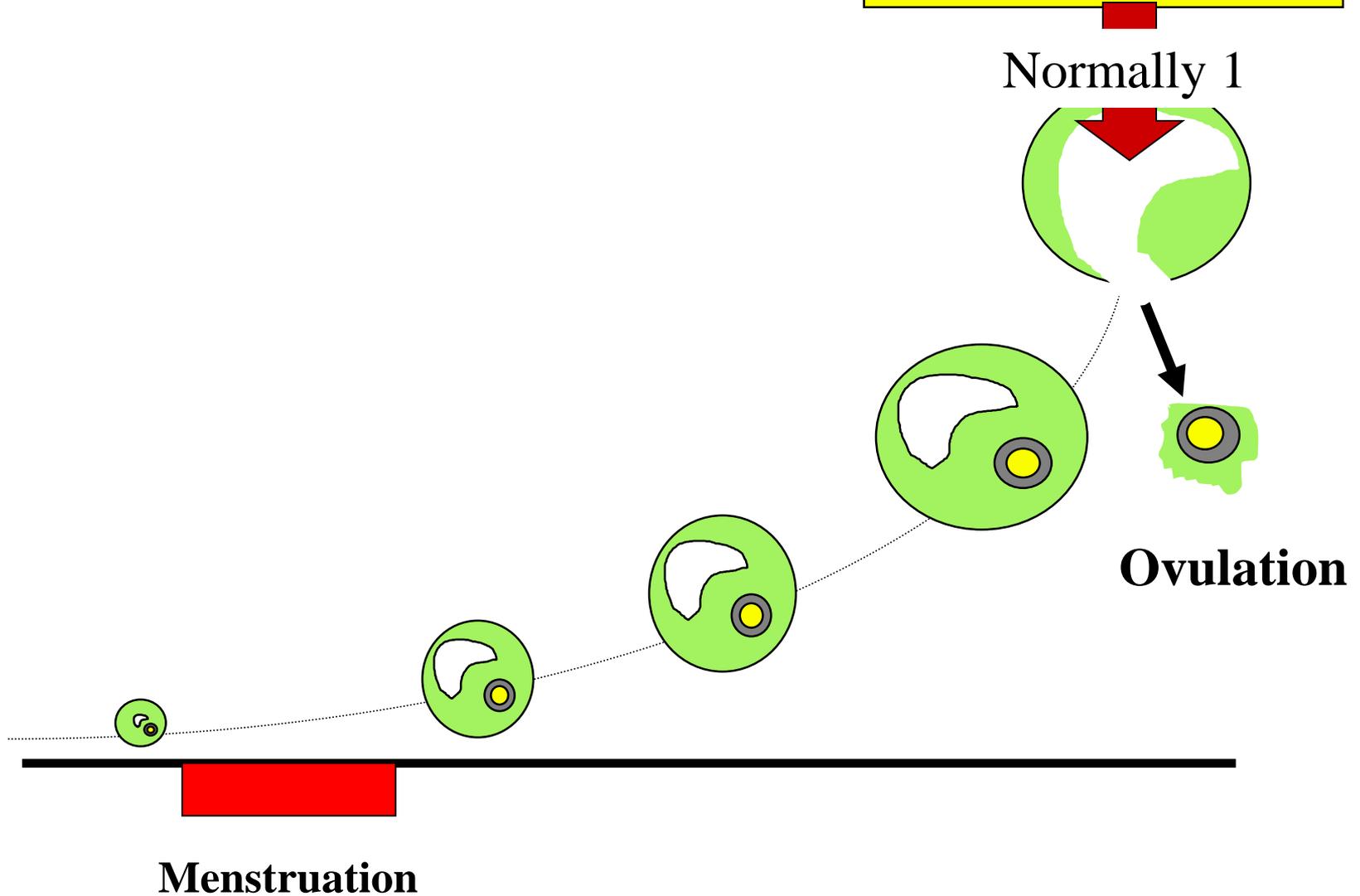
Figure 2 Growth and maturation of the human ovarian follicle from the primordial to the preovulatory stage

Growth of follicles:



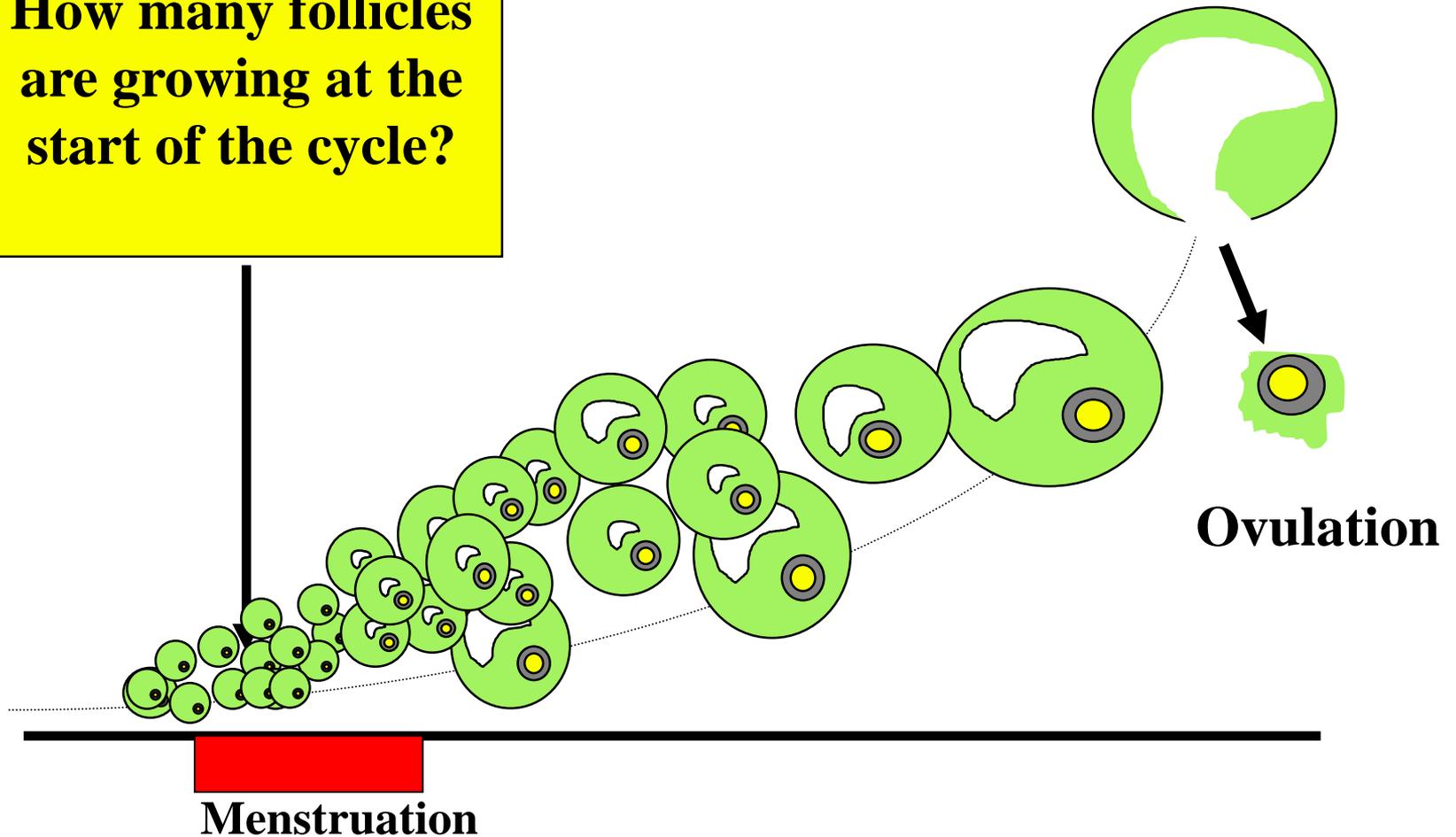
Lets look at follicular growth first...
There are a number of questions to ask...

How many follicles reach this point?



Many! 30-50

How many follicles are growing at the start of the cycle?

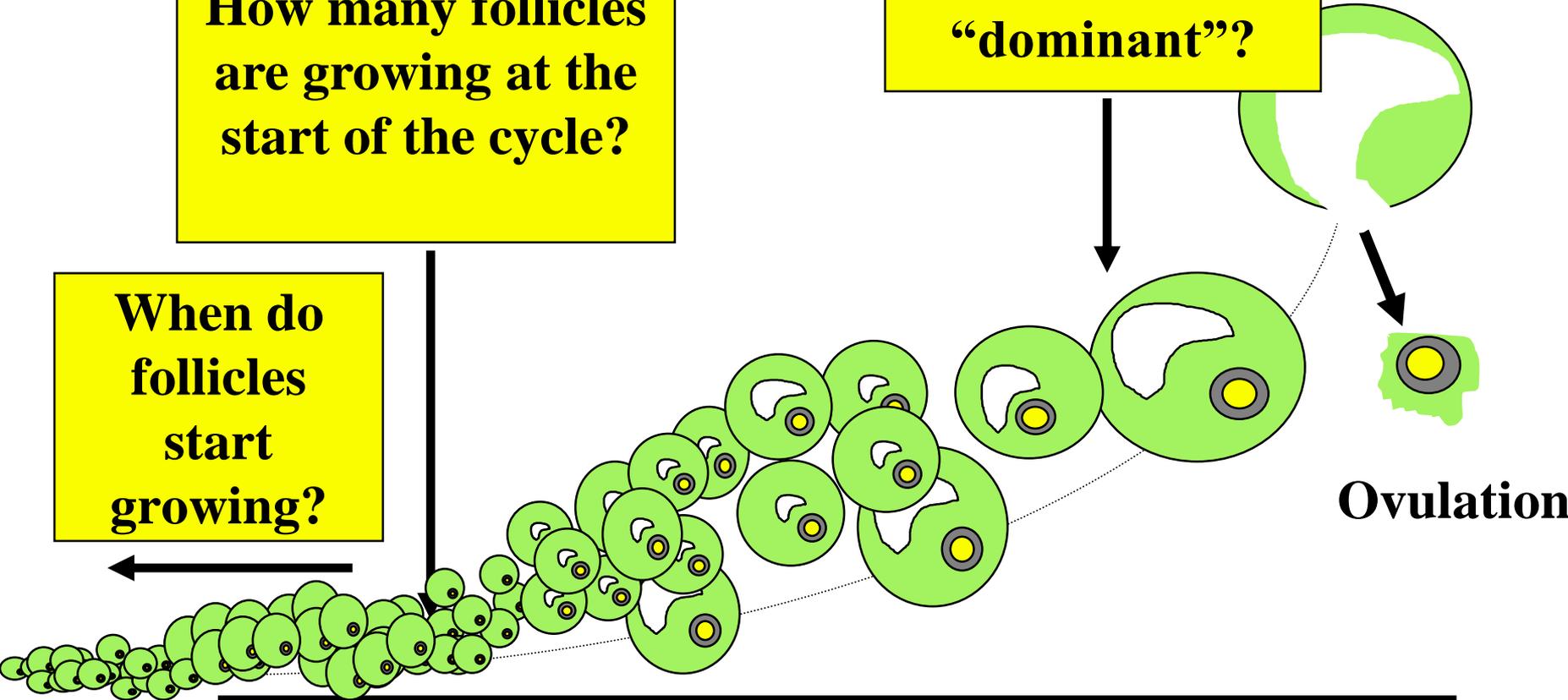


Many! 30-50

How many follicles are growing at the start of the cycle?

Why is only 1 selected and becomes “dominant”?

When do follicles start growing?



2-3 months earlier!

Menstruation

Ovulation

**What controls
follicular
growth?**

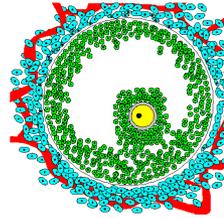
Hypothalamus

GnRH (gonadotrophin
releasing hormone)

Pituitary

LH
FSH (“gonadotrophins”)

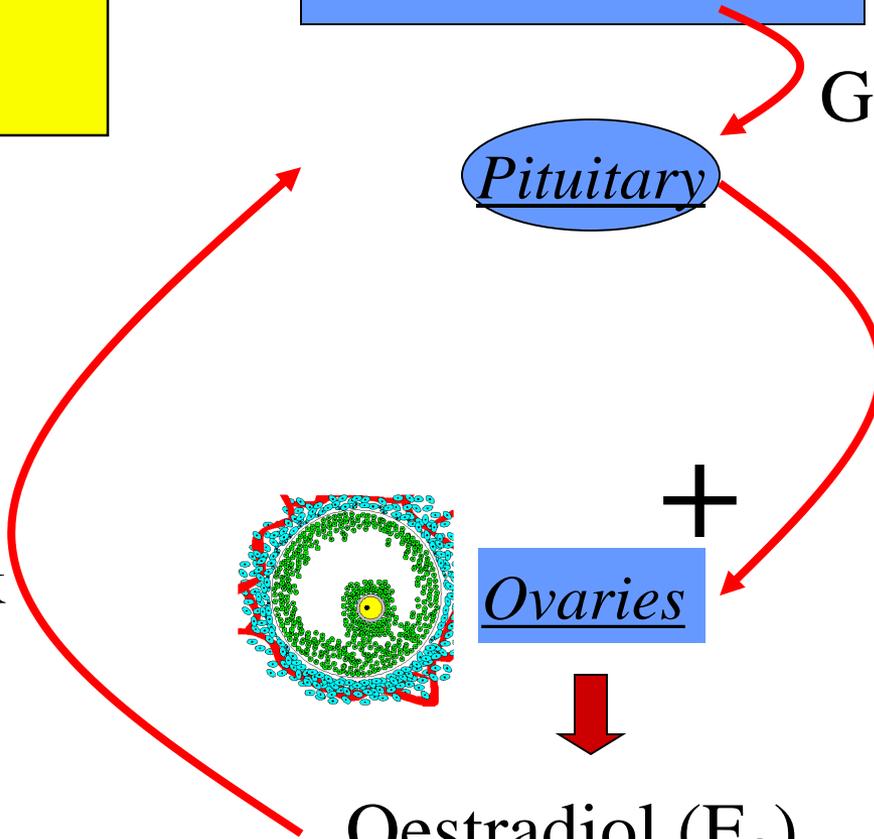
Steroid
feedback



Ovaries

Oestradiol (E_2)

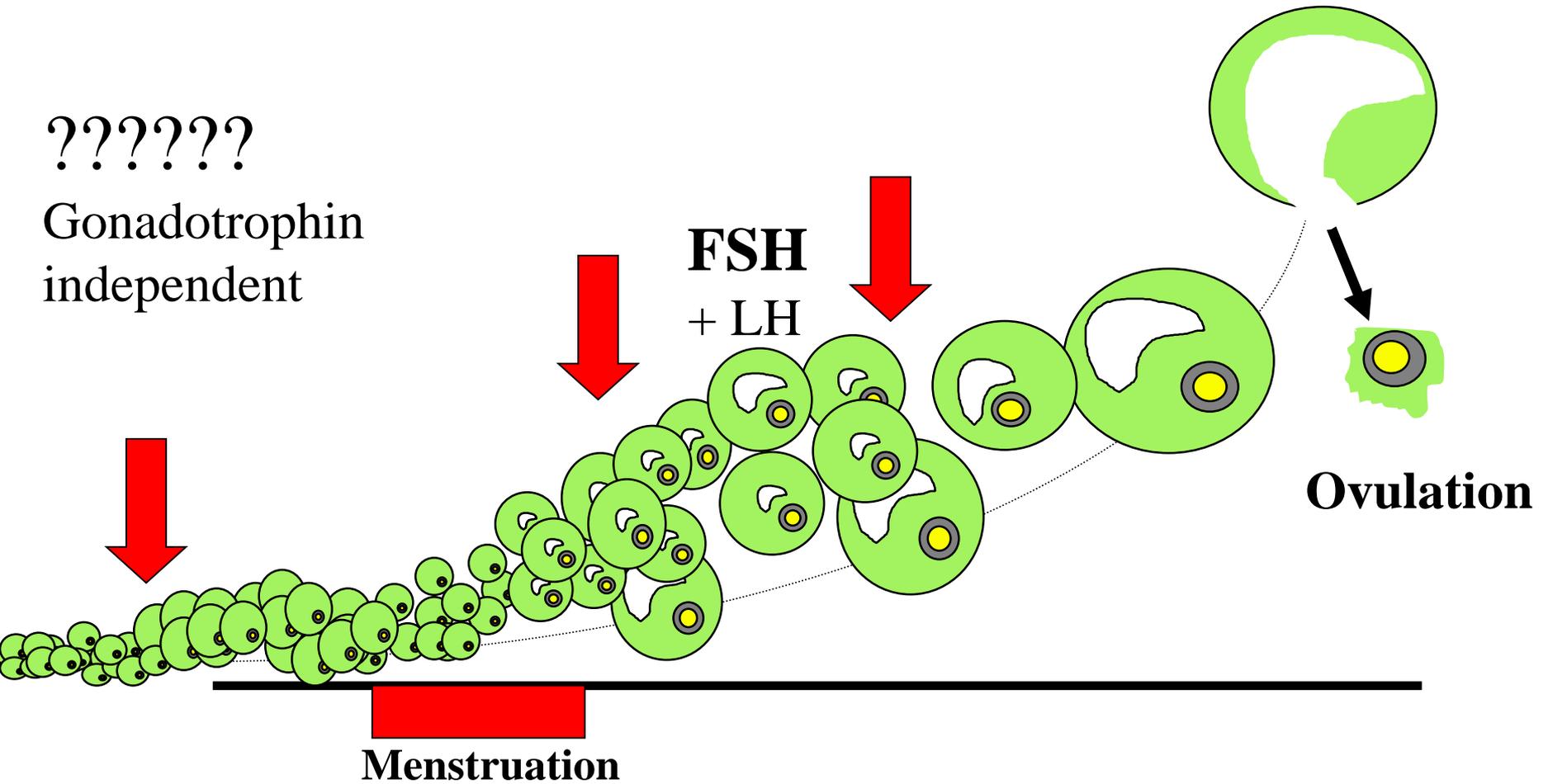
Reproductive tract
Other targets



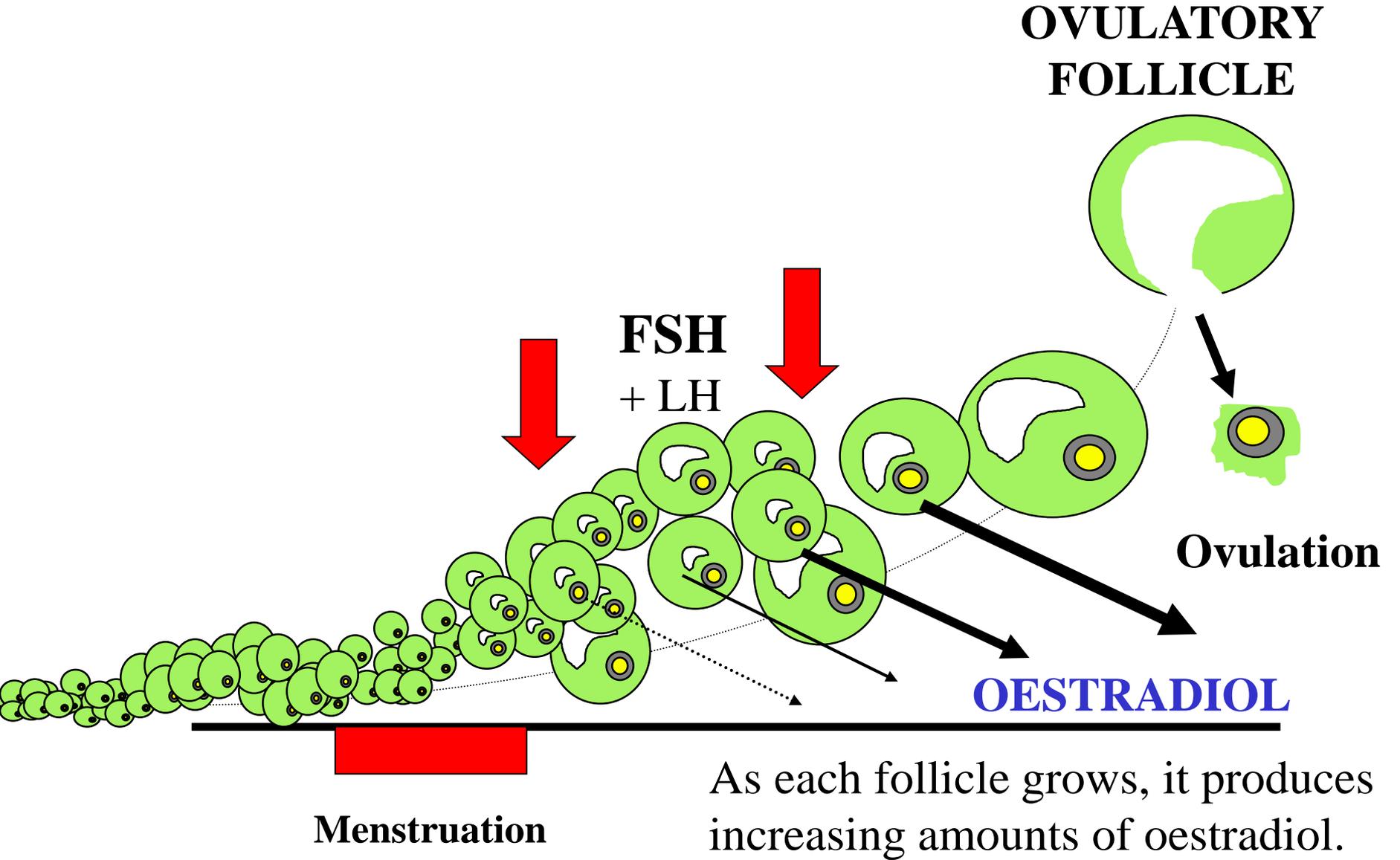
**What controls
follicular growth?**

???????

Gonadotrophin
independent



Fase Gonadotr.indip.è continua per tutta la vita della donna,regolata da fattori di regolazione intraovarici
AMH regola reclutamento dei follicoli primordiali (prodotto da preantrali e antrali precoci)



OVULATORY FOLLICLE

FSH + LH

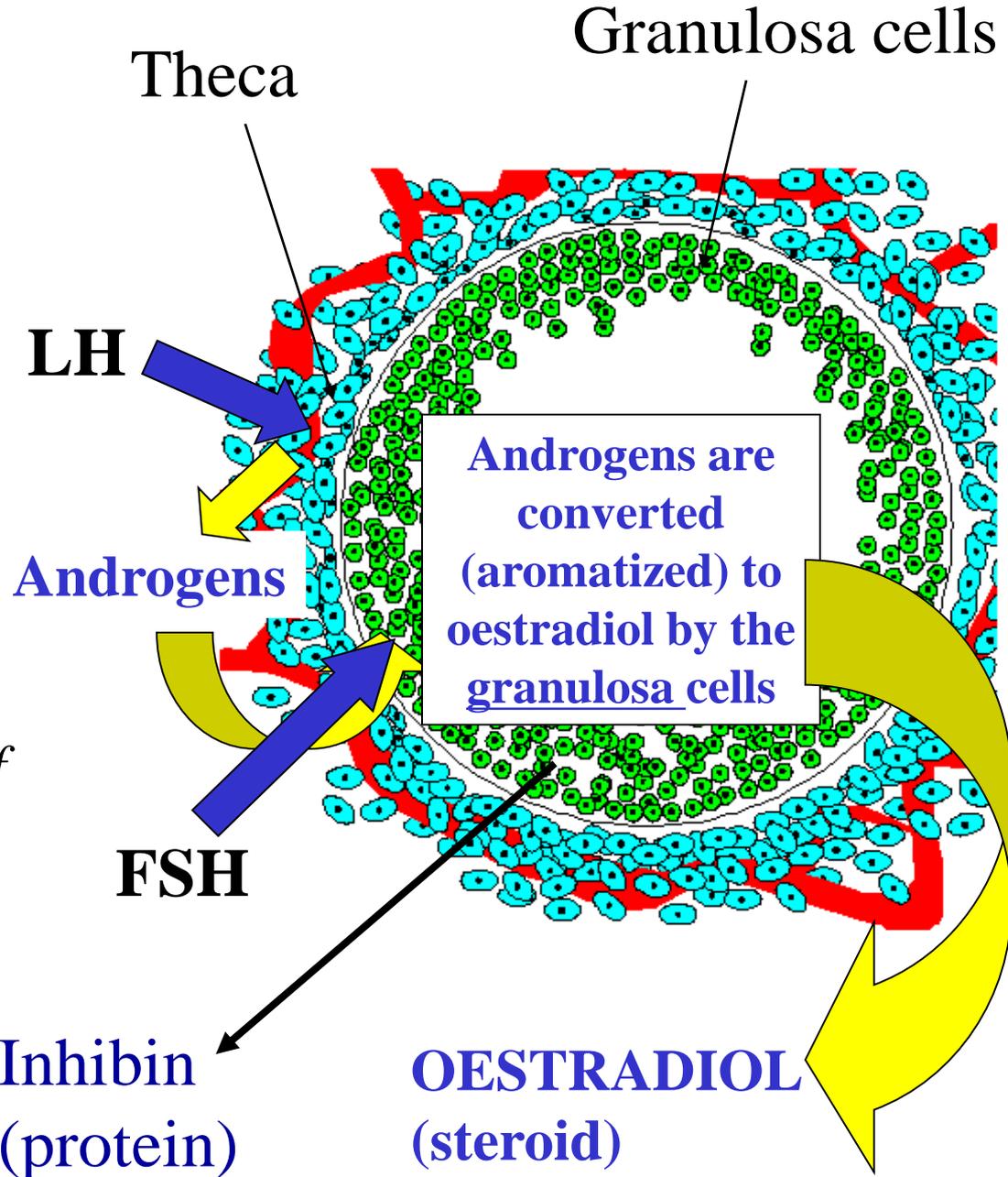
Ovulation

OESTRADIOL

Menstruation

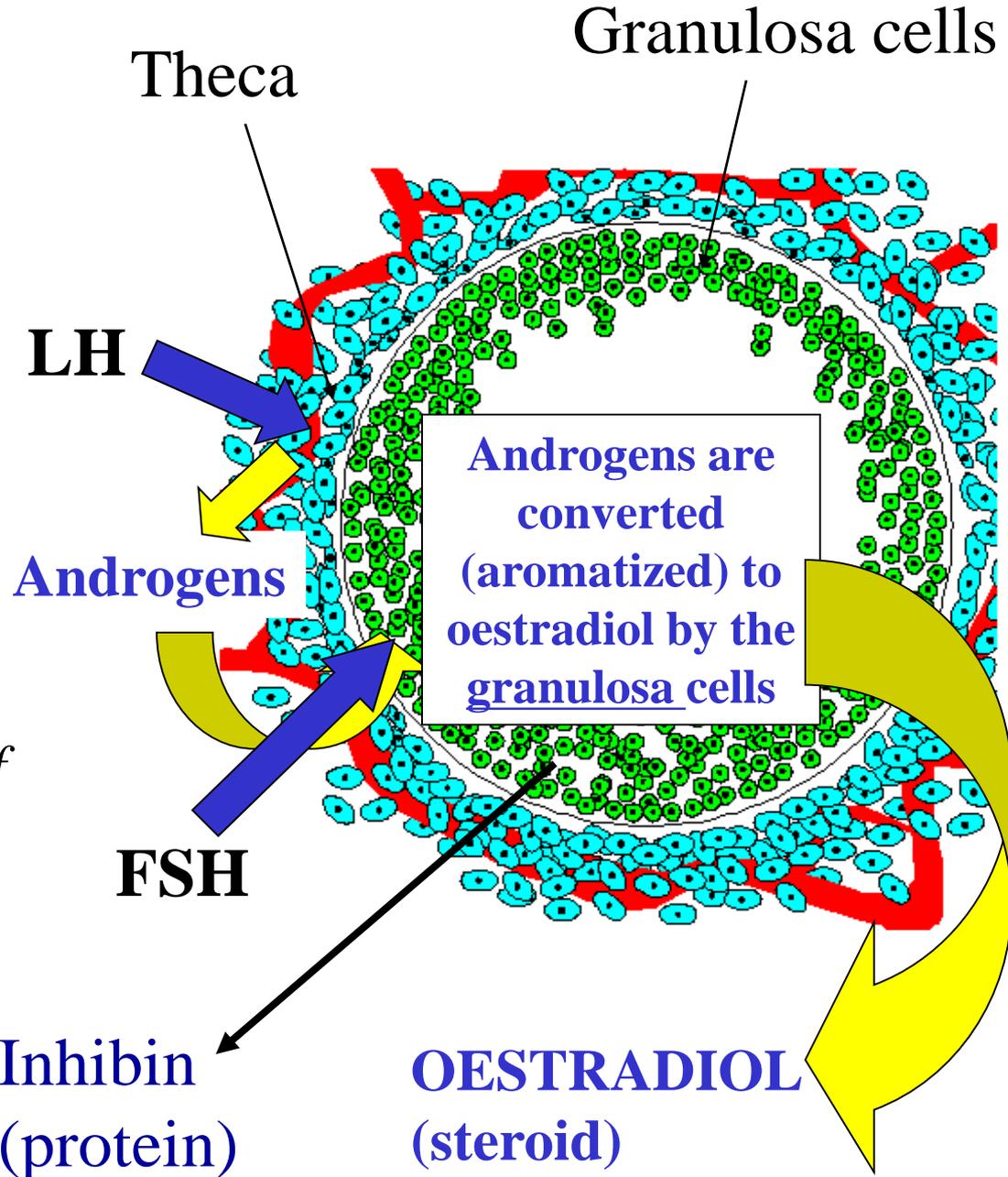
As each follicle grows, it produces increasing amounts of oestradiol.

How is oestradiol production controlled ?

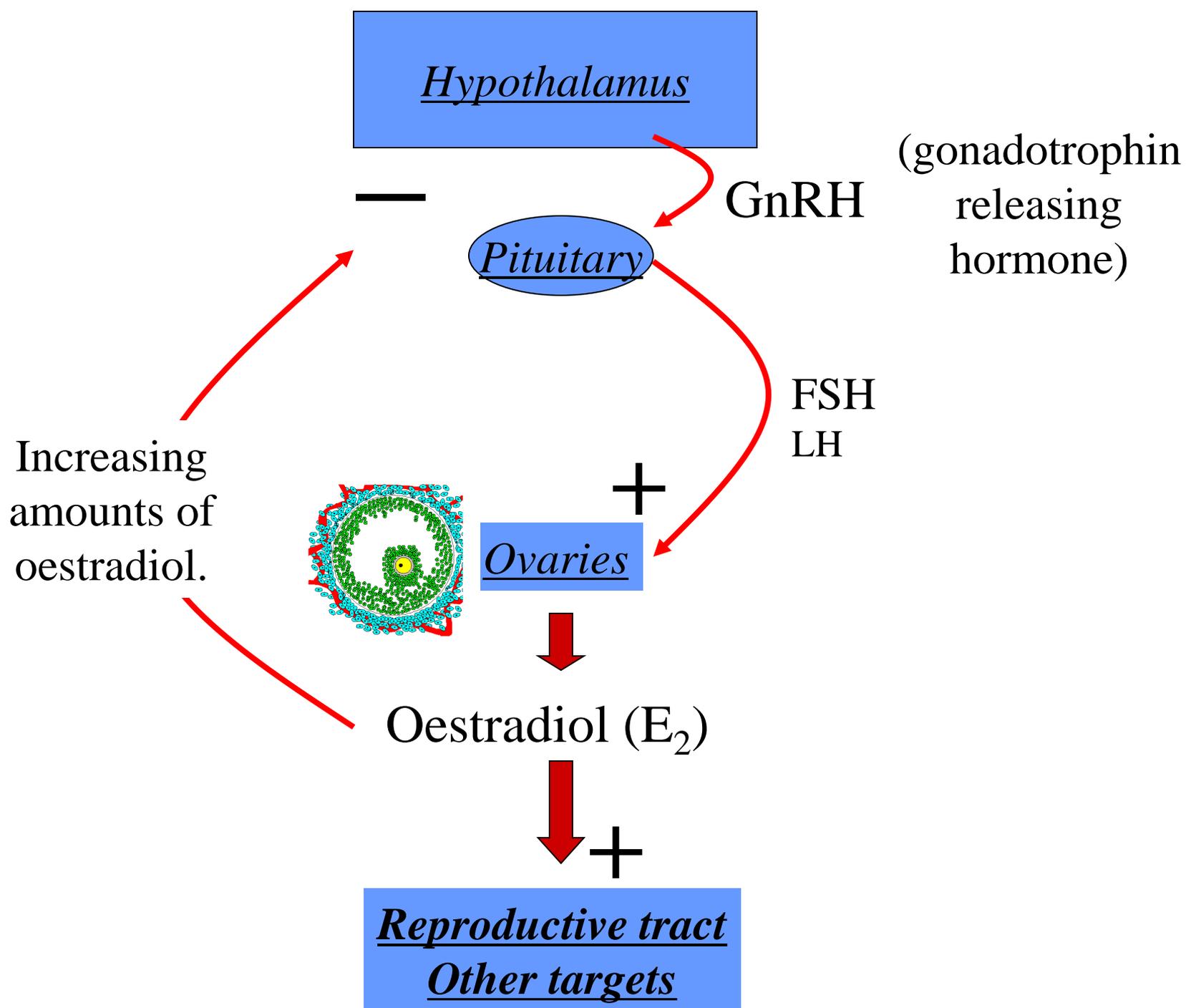


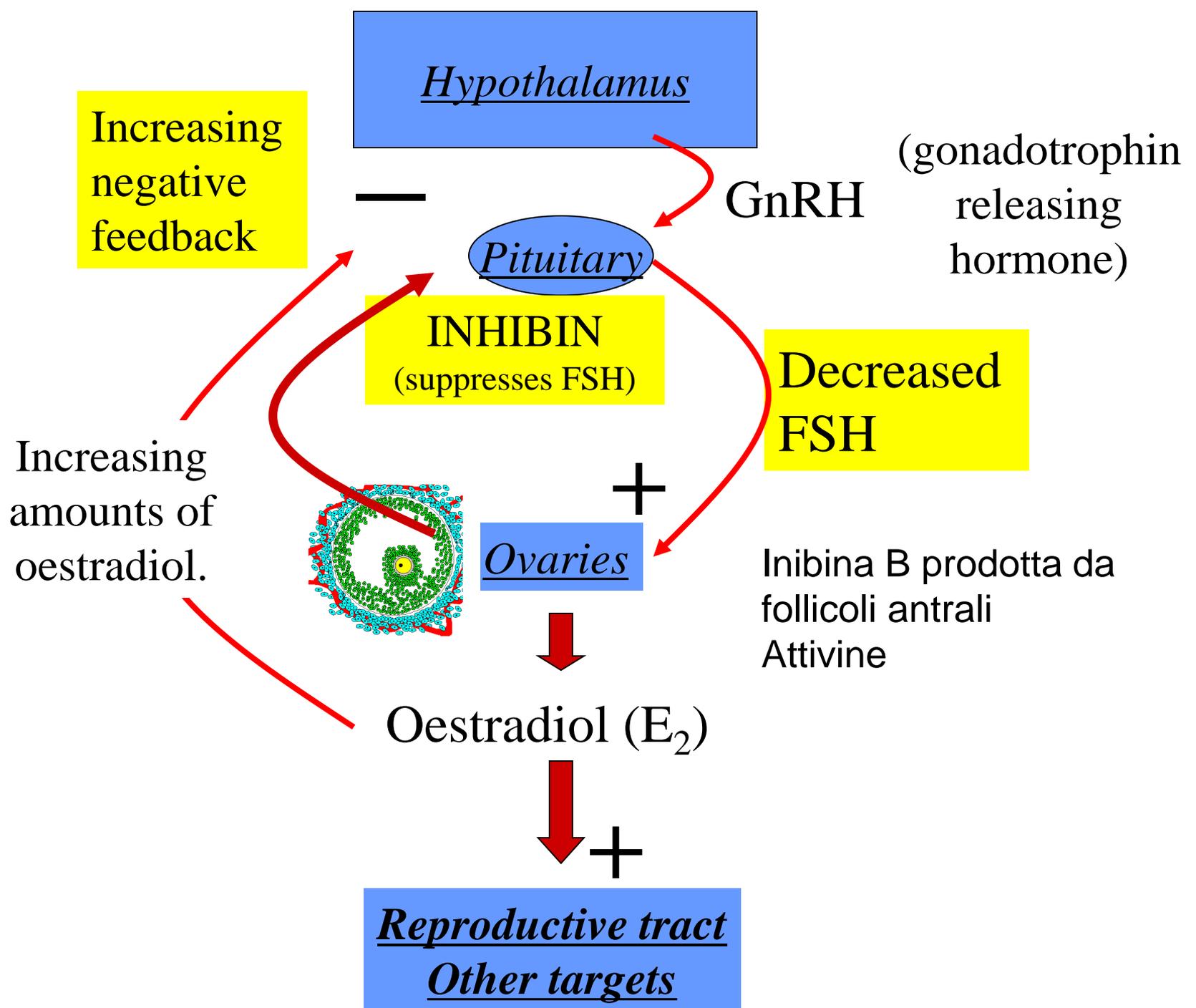
(Note: the production of androgens is a normal part of ovarian physiology)

How is oestradiol production controlled ?

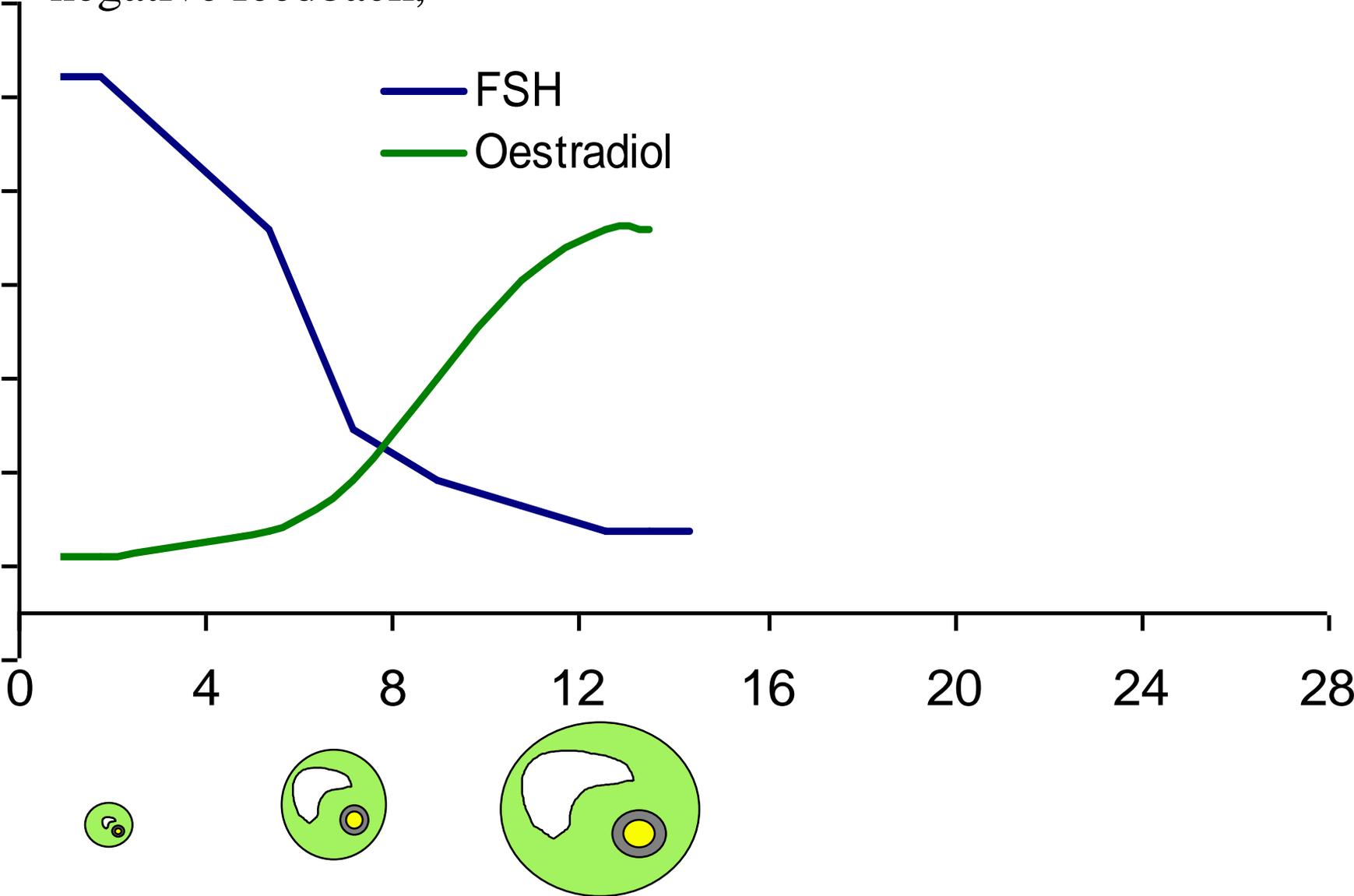


(Note: the production of androgens is a normal part of ovarian physiology)

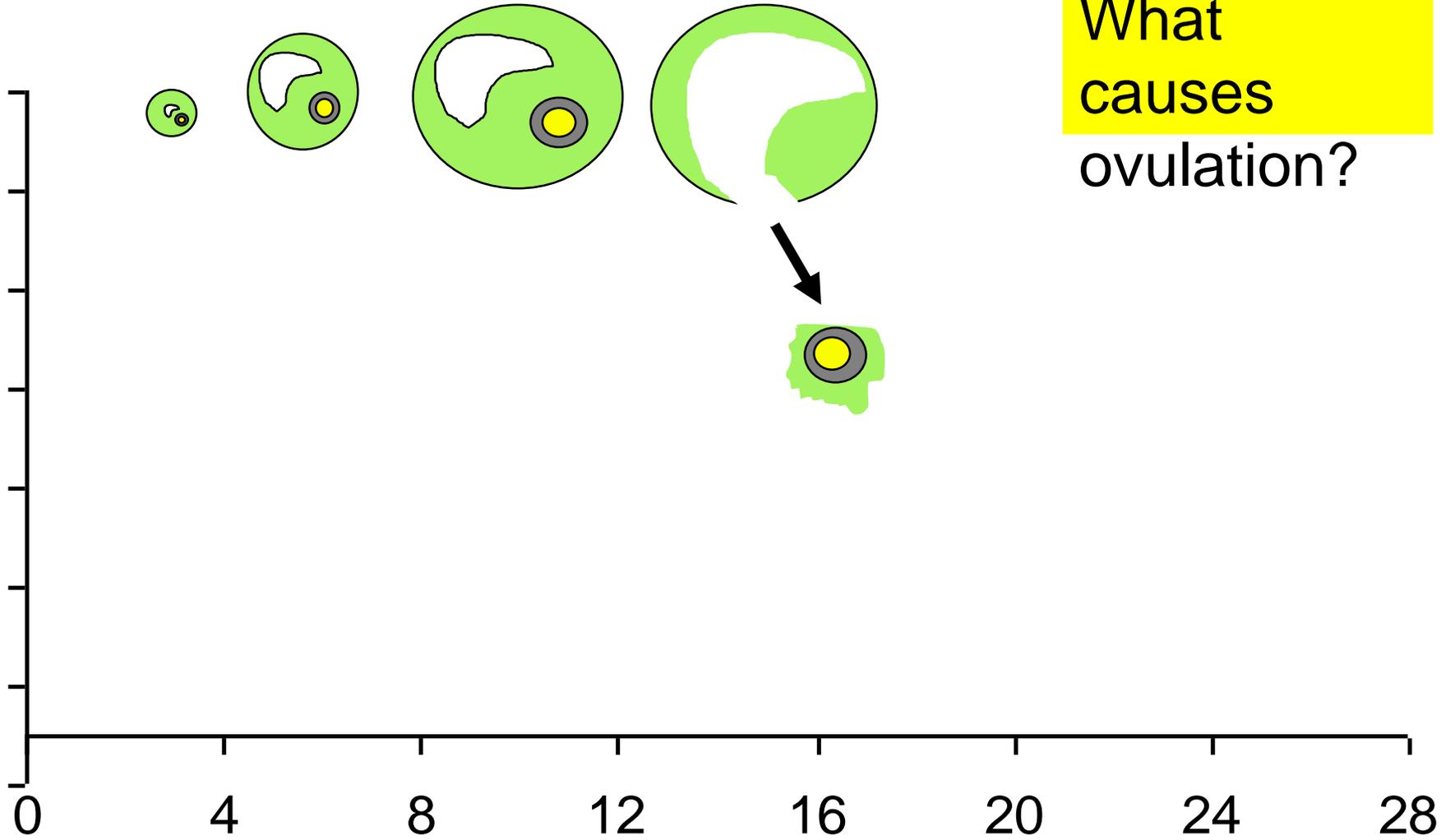




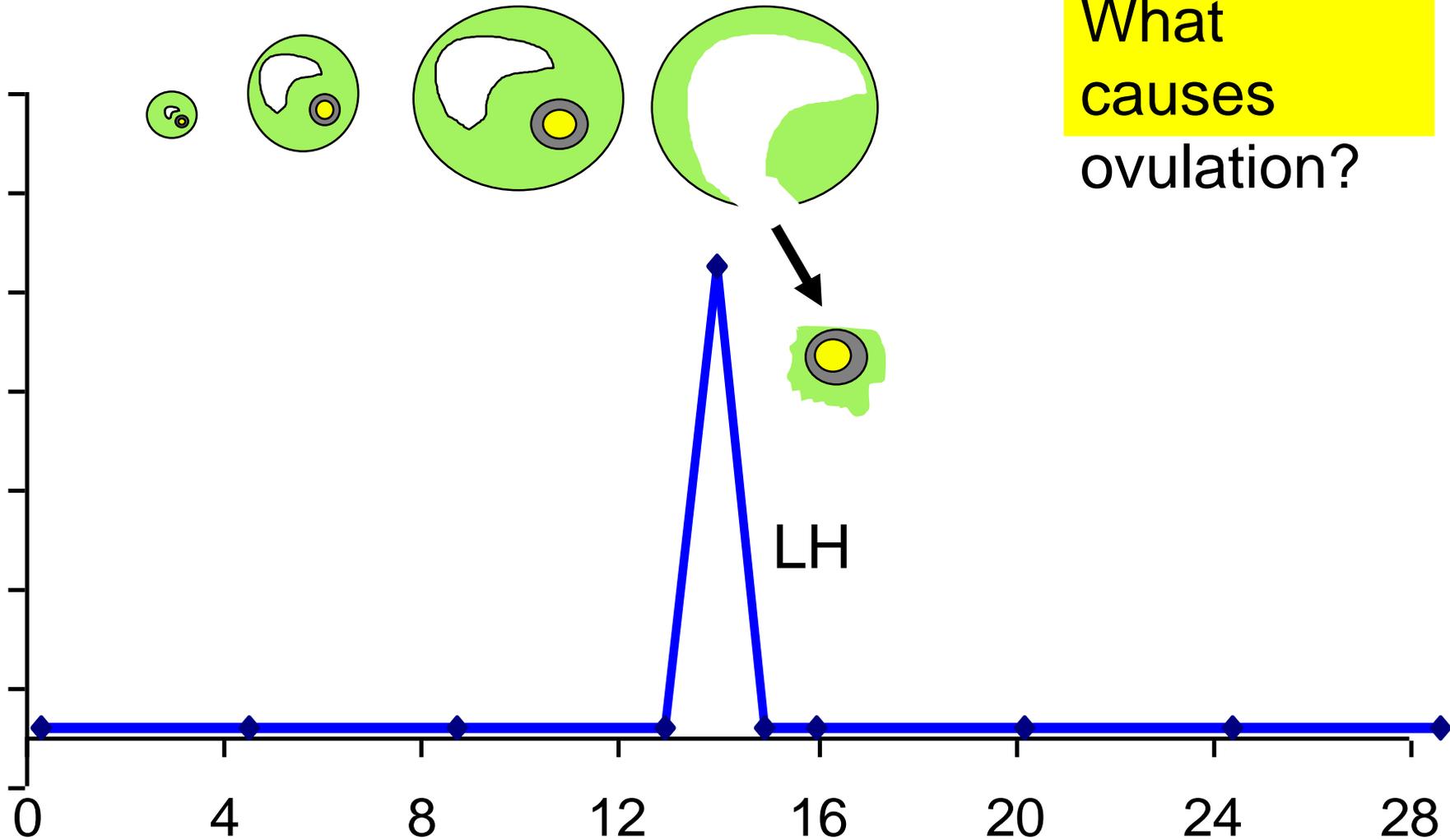
As the follicles grow, FSH levels fall due to the negative feedback,



What
causes
ovulation?

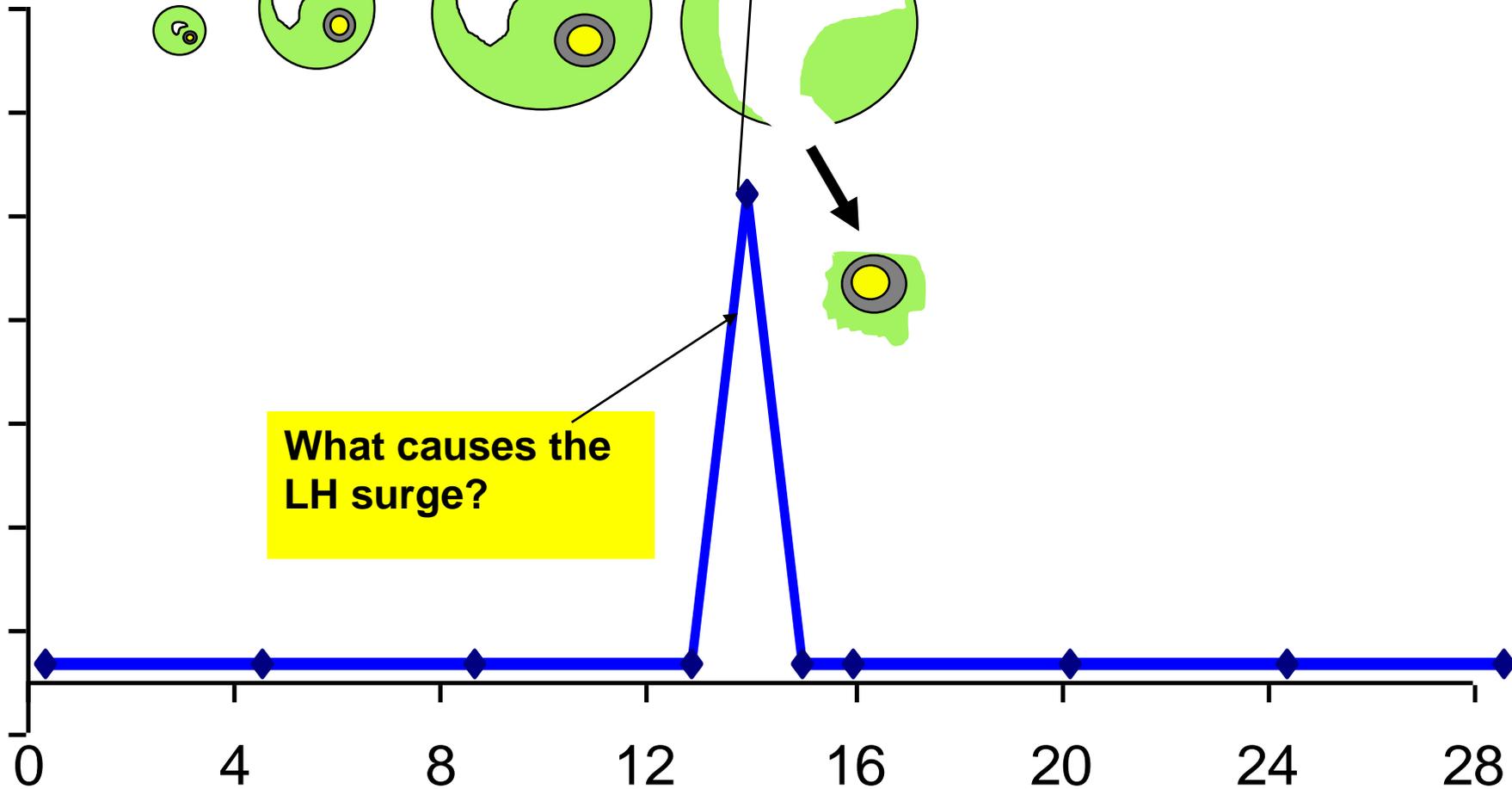


What causes ovulation?



What effects does it have?

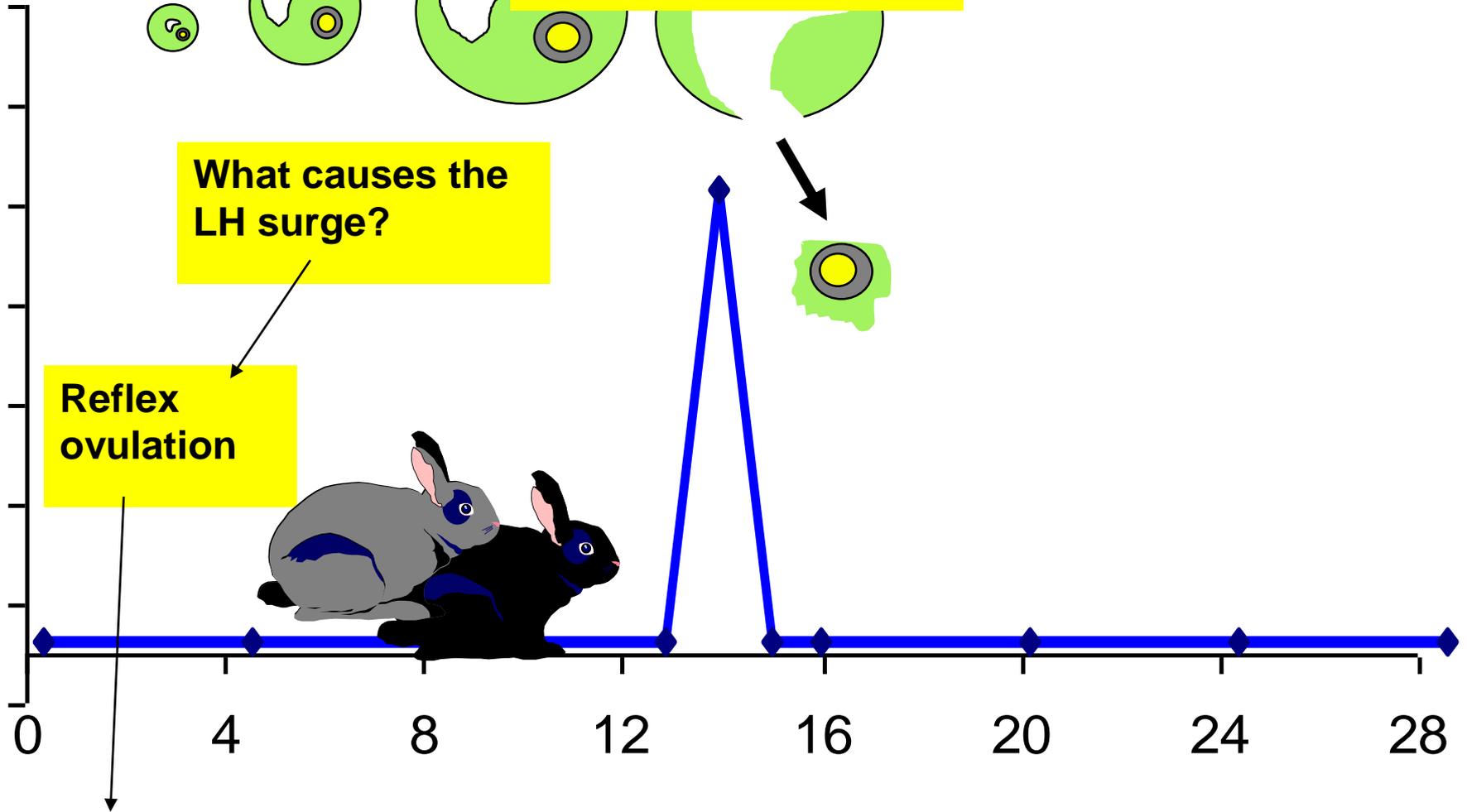
What causes the LH surge?



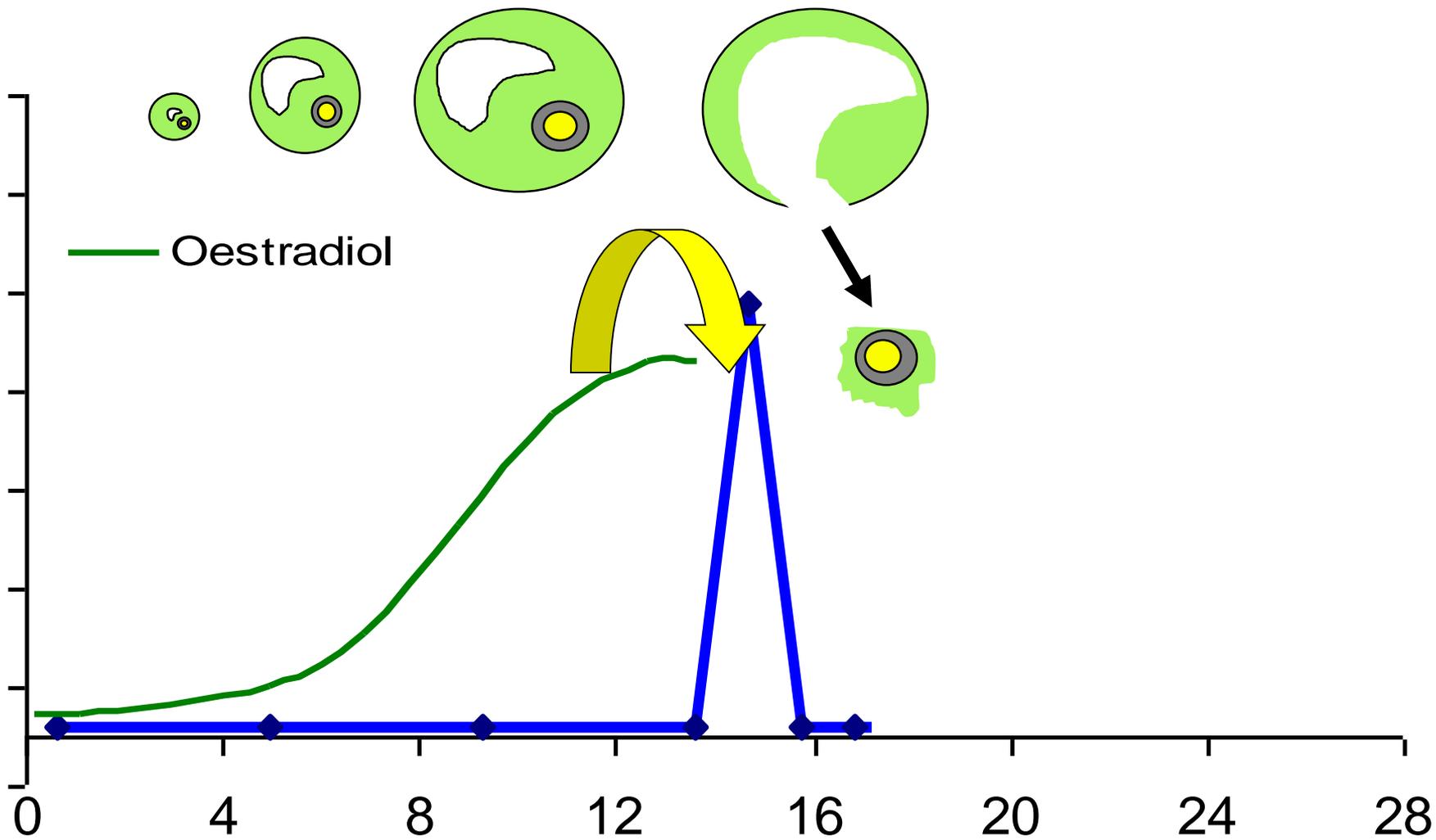
NOT
HUMANS!

What causes the
LH surge?

Reflex
ovulation

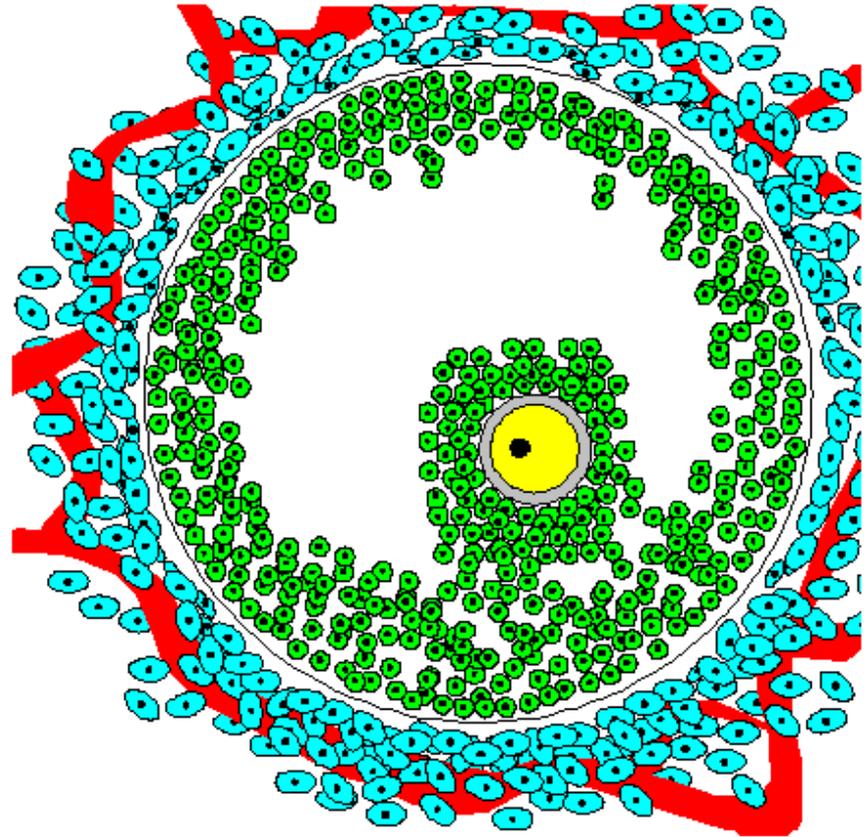


Mating → Neuroendocrine reflex → LH →



How does the LH surge affect the follicle?

About 36 h between LH surge and oocyte release.....

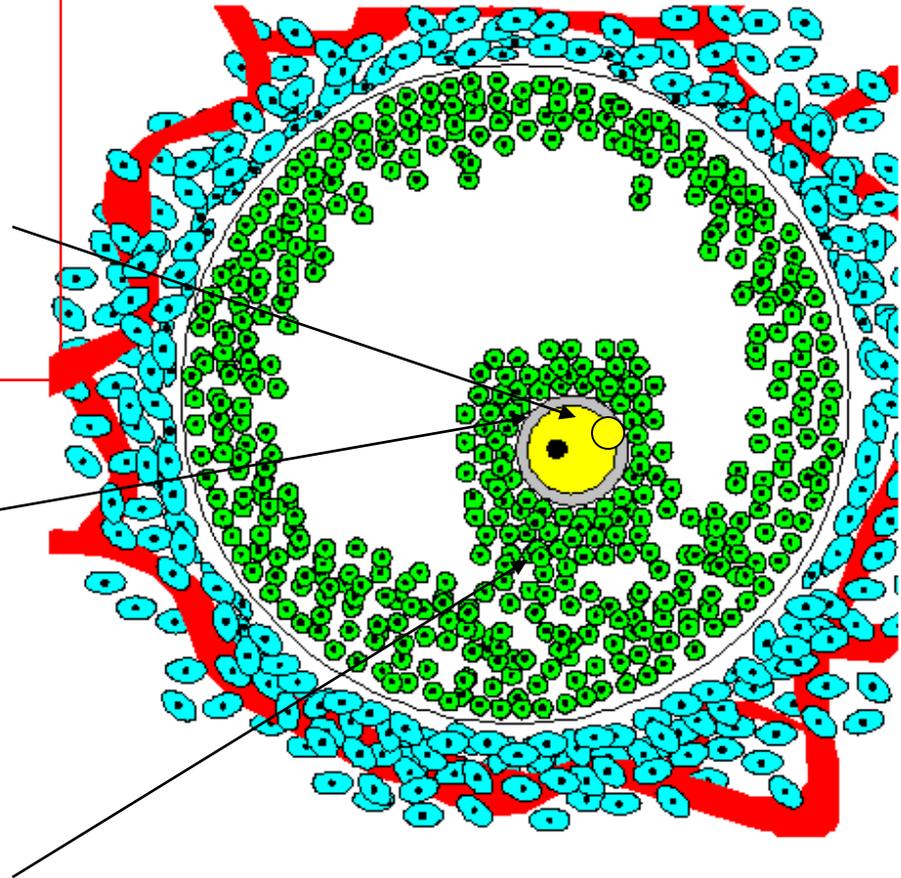


Oocyte:

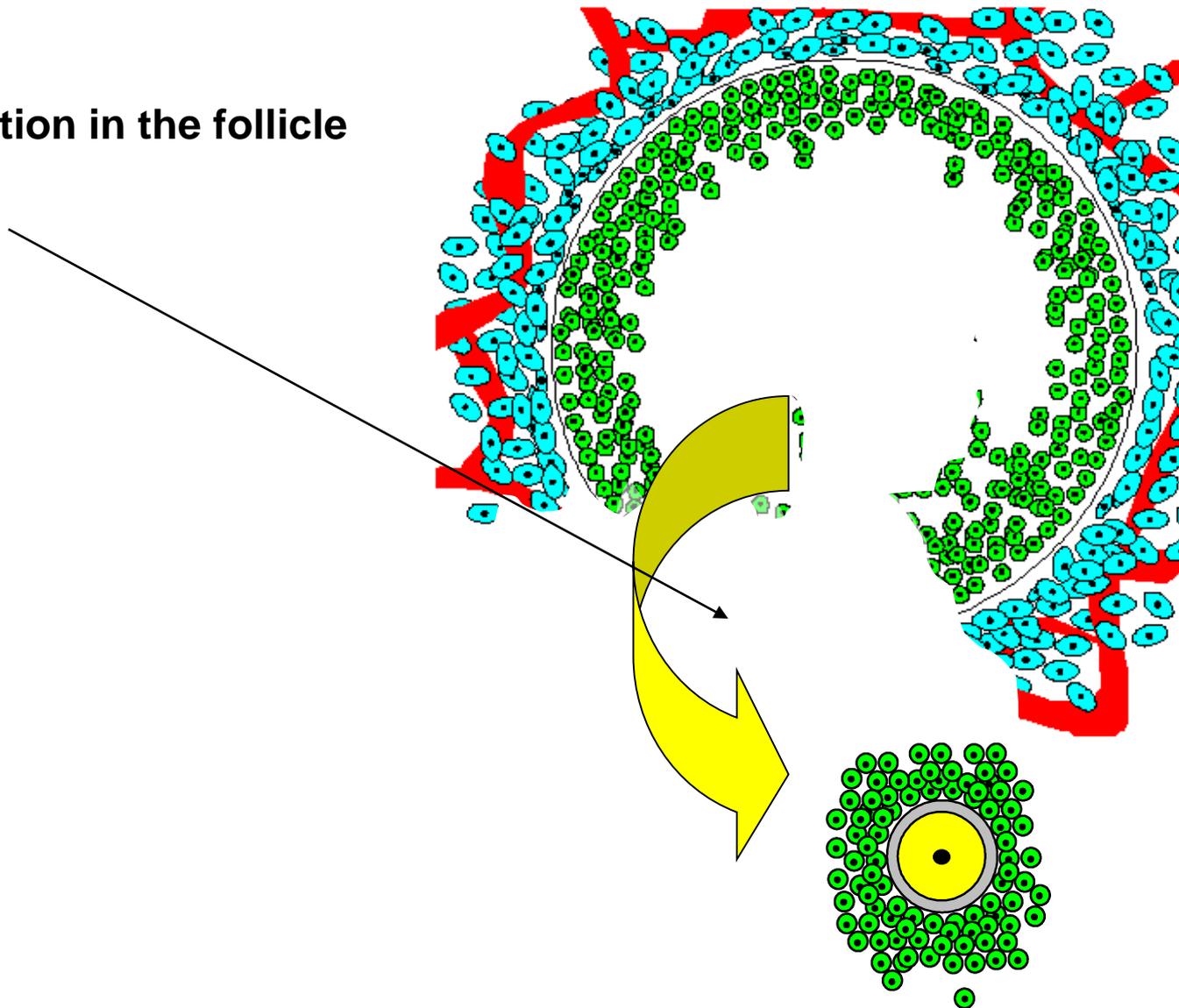
- Completion of the 1st meiotic division (unequal division; extrusion of 1st polar body)
- 2nd meiotic division starts but becomes arrested before completion.

Microvilli across the zona pellucida are withdrawn.

Loosening of cumulus cells

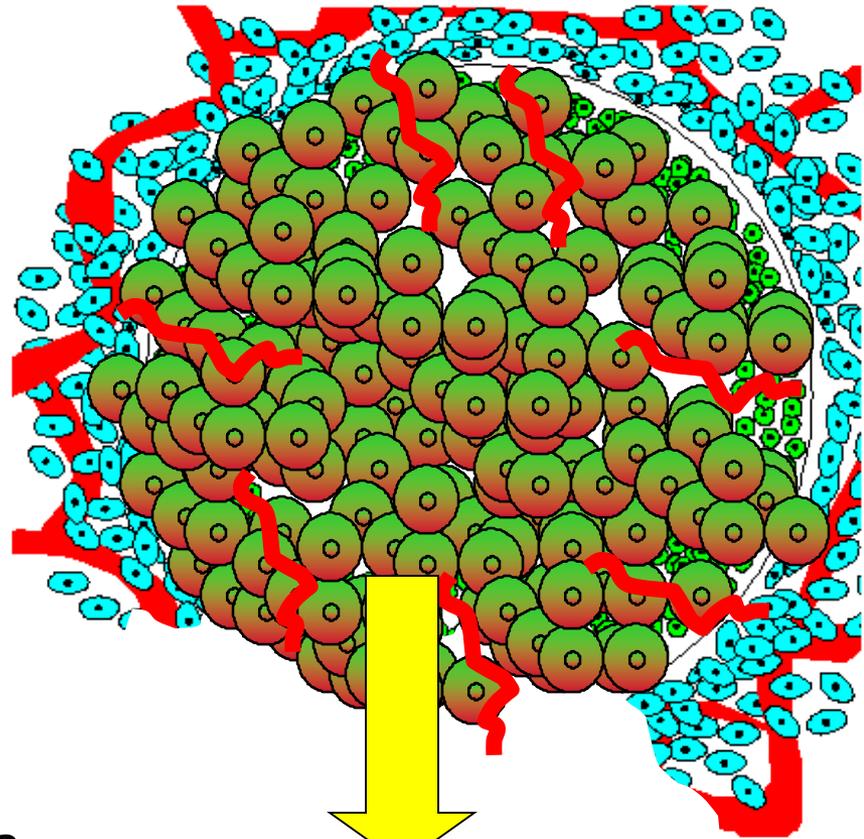


Enzyme induction in the follicle wall



Transformation of ruptured follicle into corpus luteum (CL)

- Ruptured follicle becomes solid corpus luteum
- Thecal cells and blood vessels invade
- Granulosa cells hypertrophy and terminally differentiate (“luteinisation”).



Steroid secretion changes –

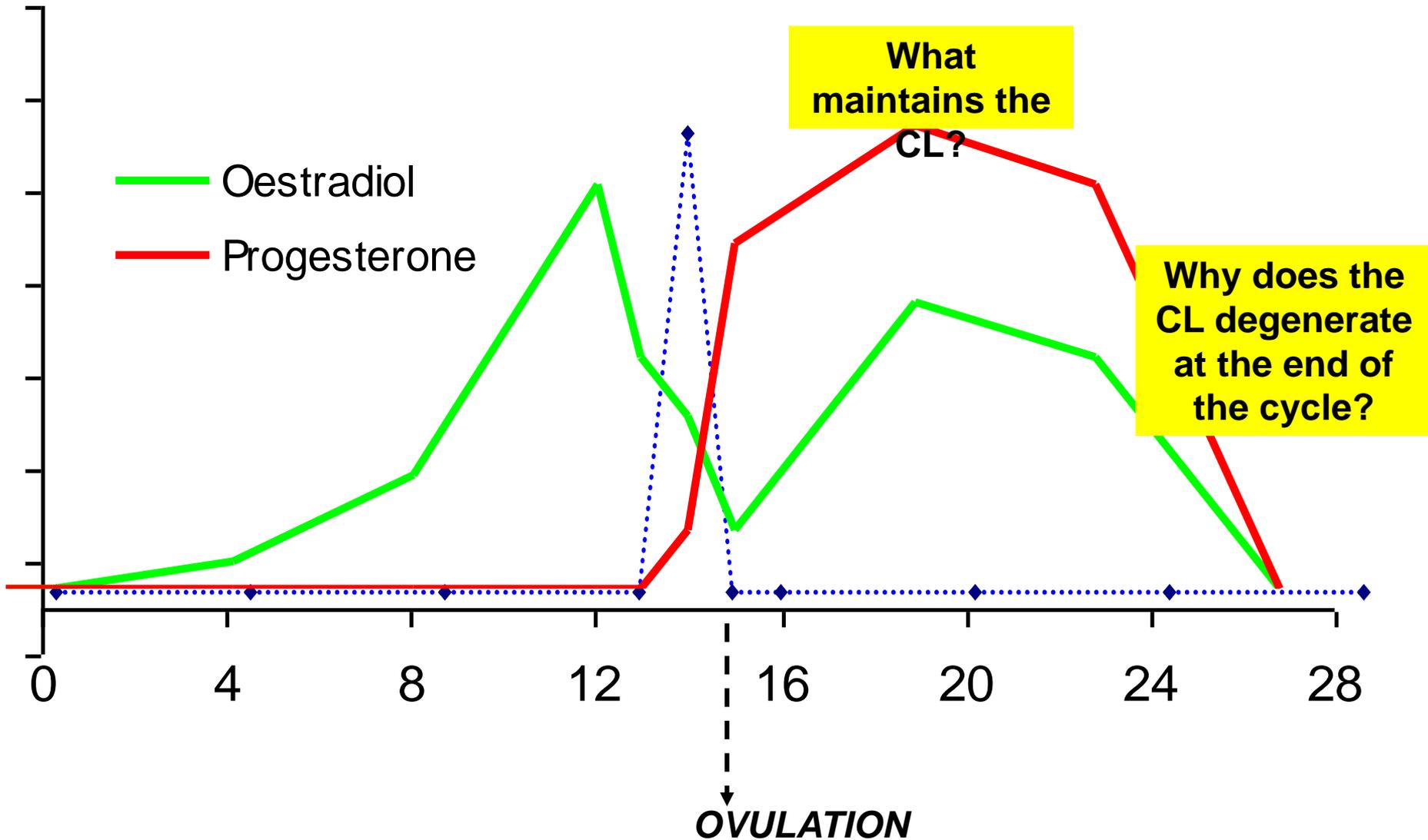
Progesterone

+

Oestradiol

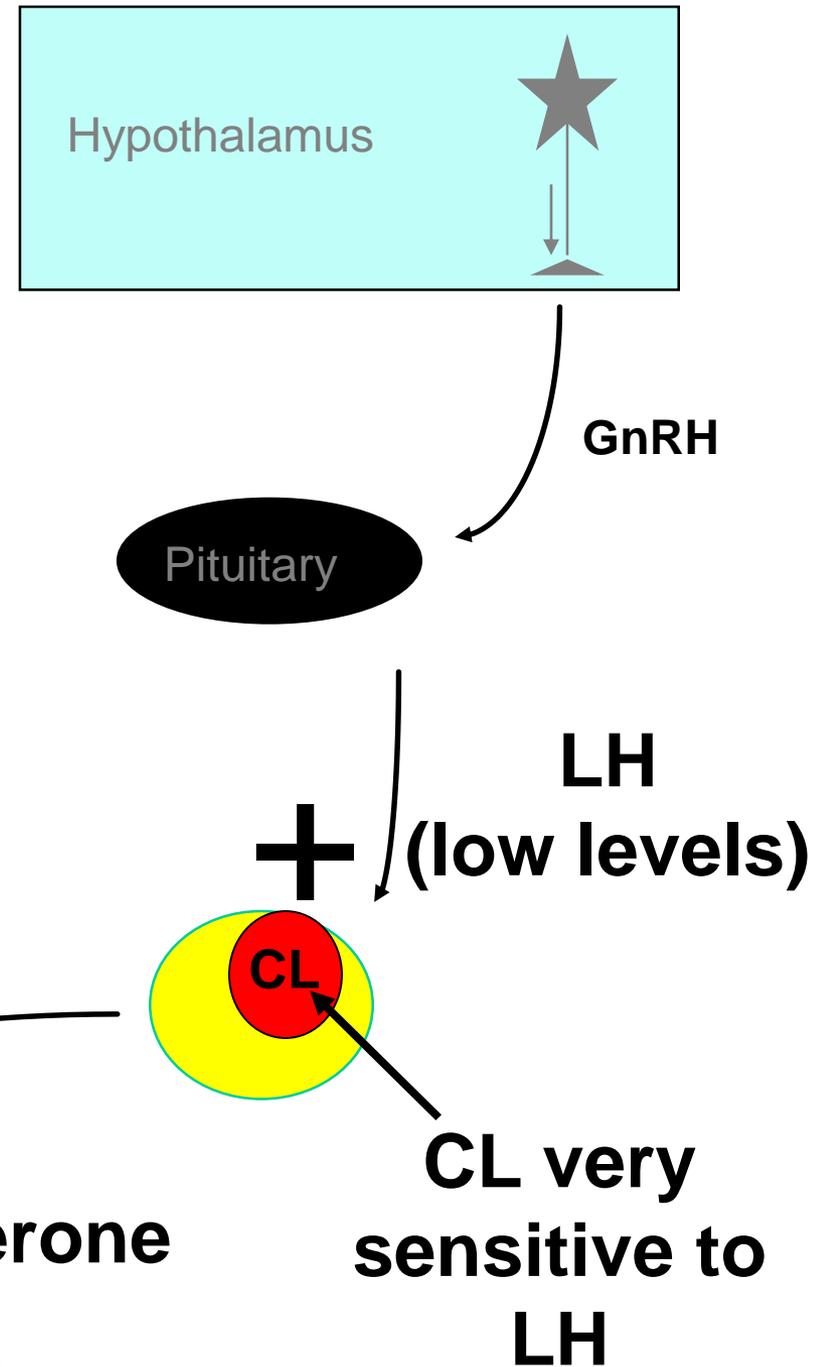
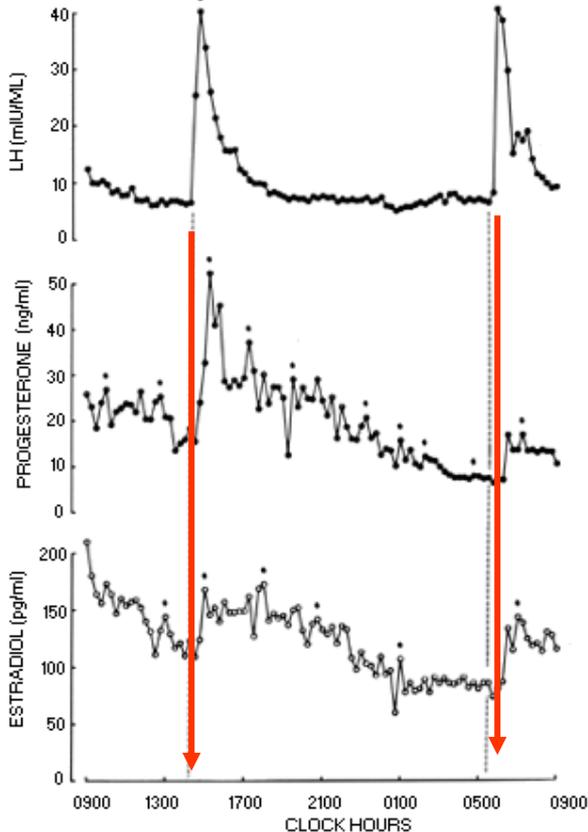
Follicular phase:
Oestradiol domination

Luteal phase:
Progesterone domination



What maintains the CL?

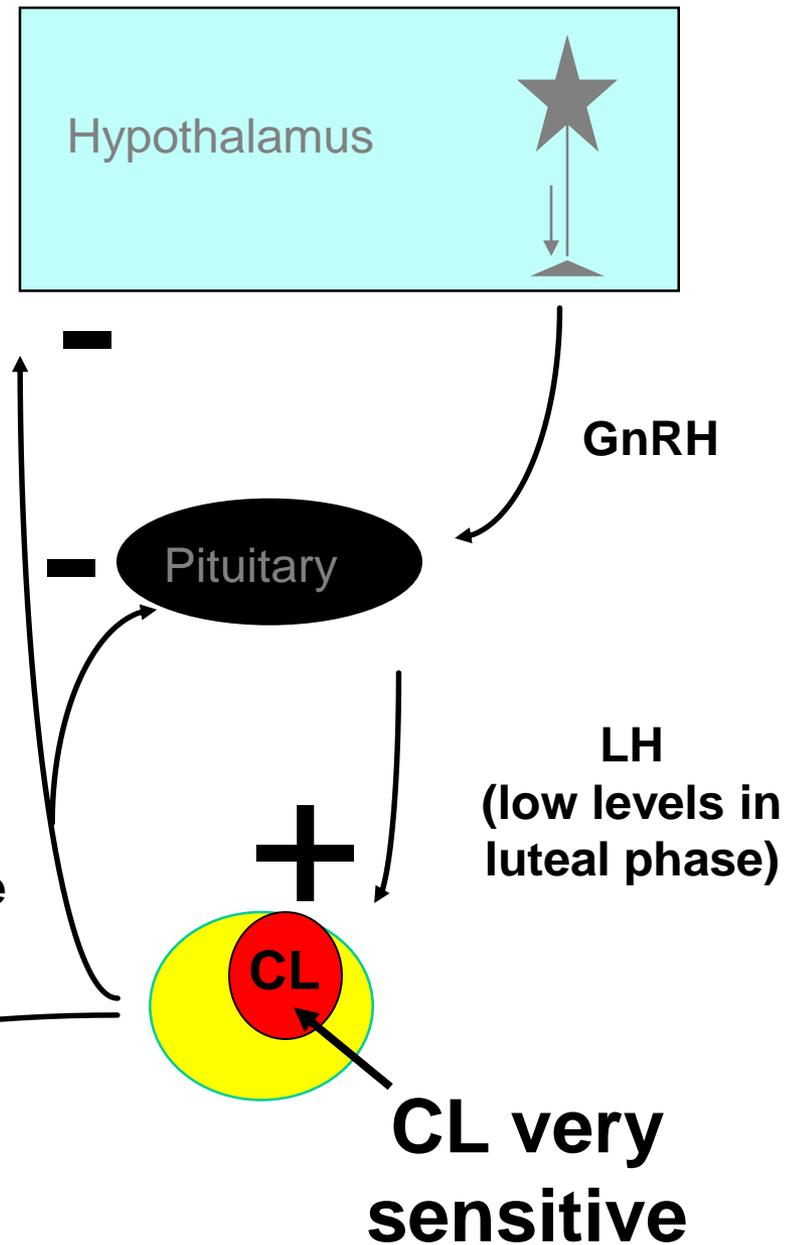
~ 8 hr
between LH
pulses



What maintains the CL?

Steroid negative feedback keeps LH and FSH levels relatively low

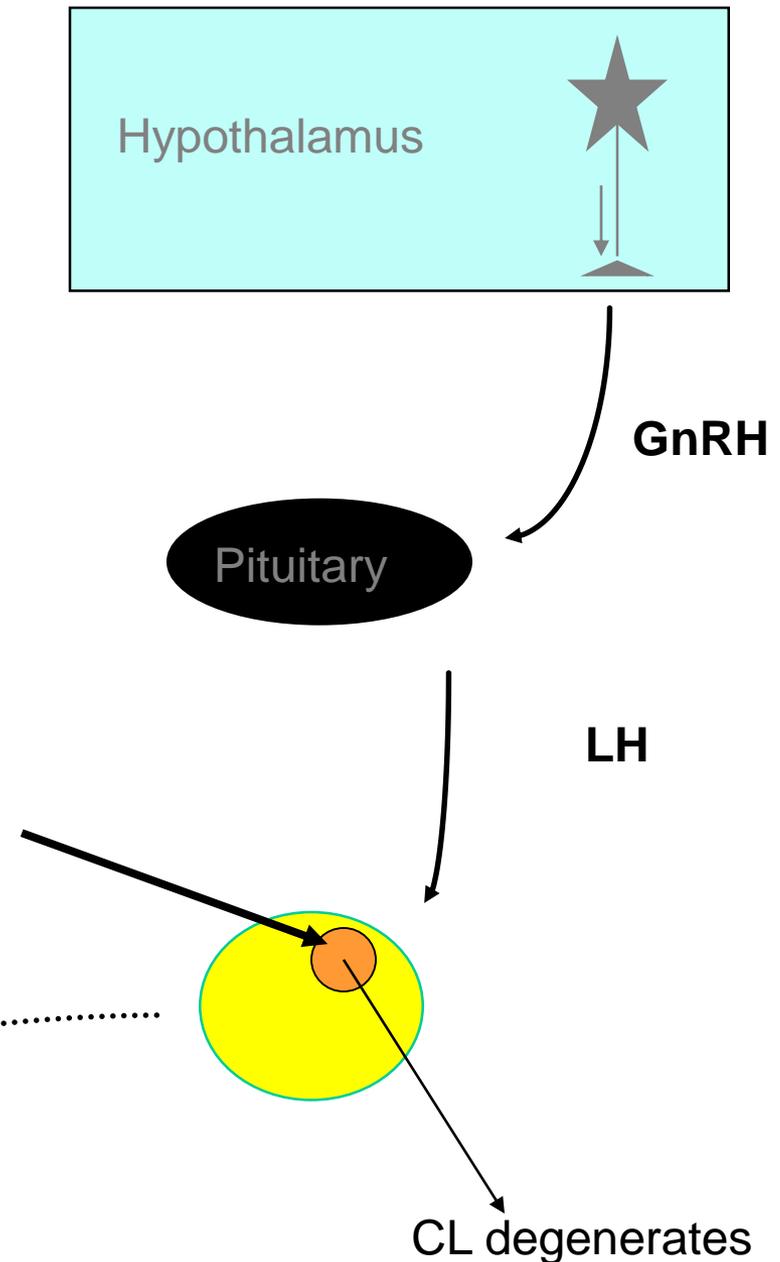
Reproductive tract etc



Towards the end of the cycle, the sensitivity to LH reduces.

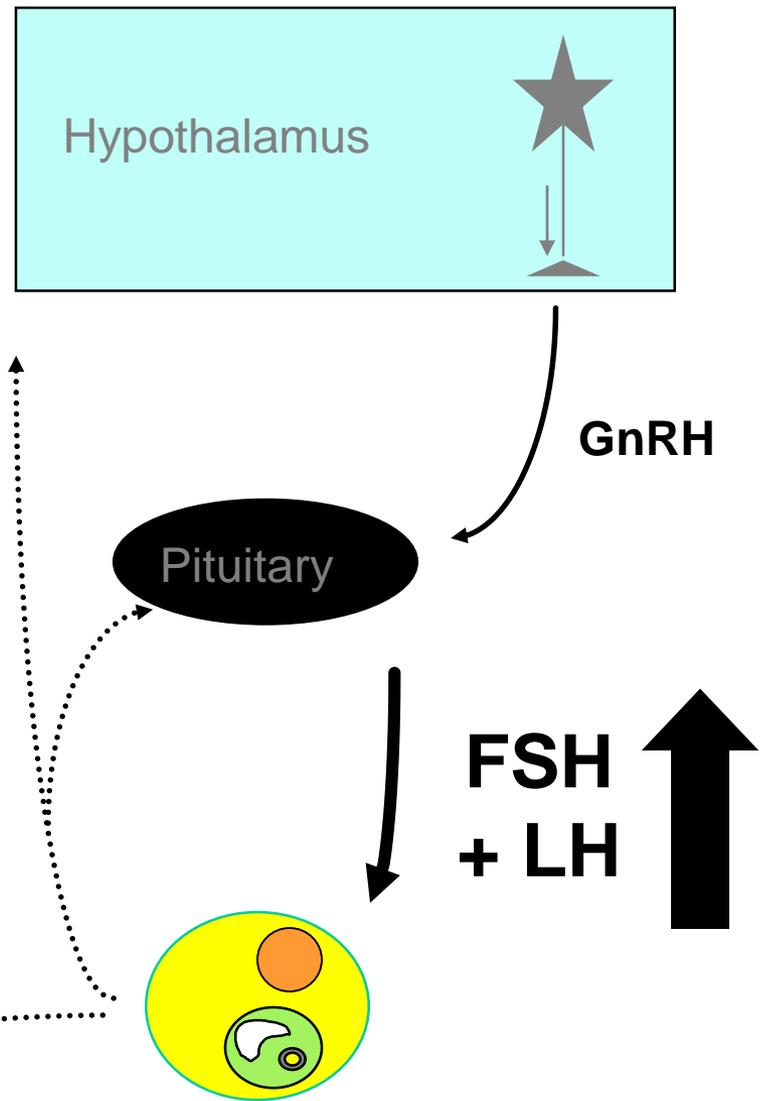
The low levels of LH are insufficient to keep the CL going

Progesterone
+ E₂



As CL degenerates...
steroid negative feedback reduces ..

Progesterone
+ E₂

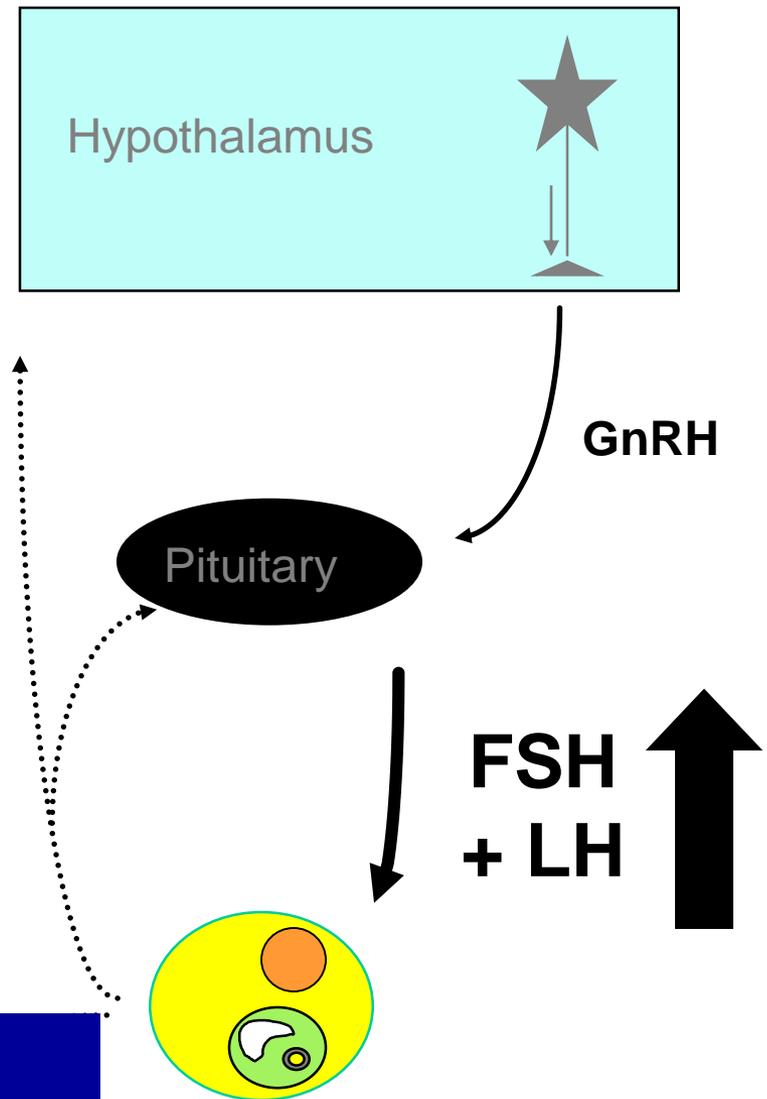


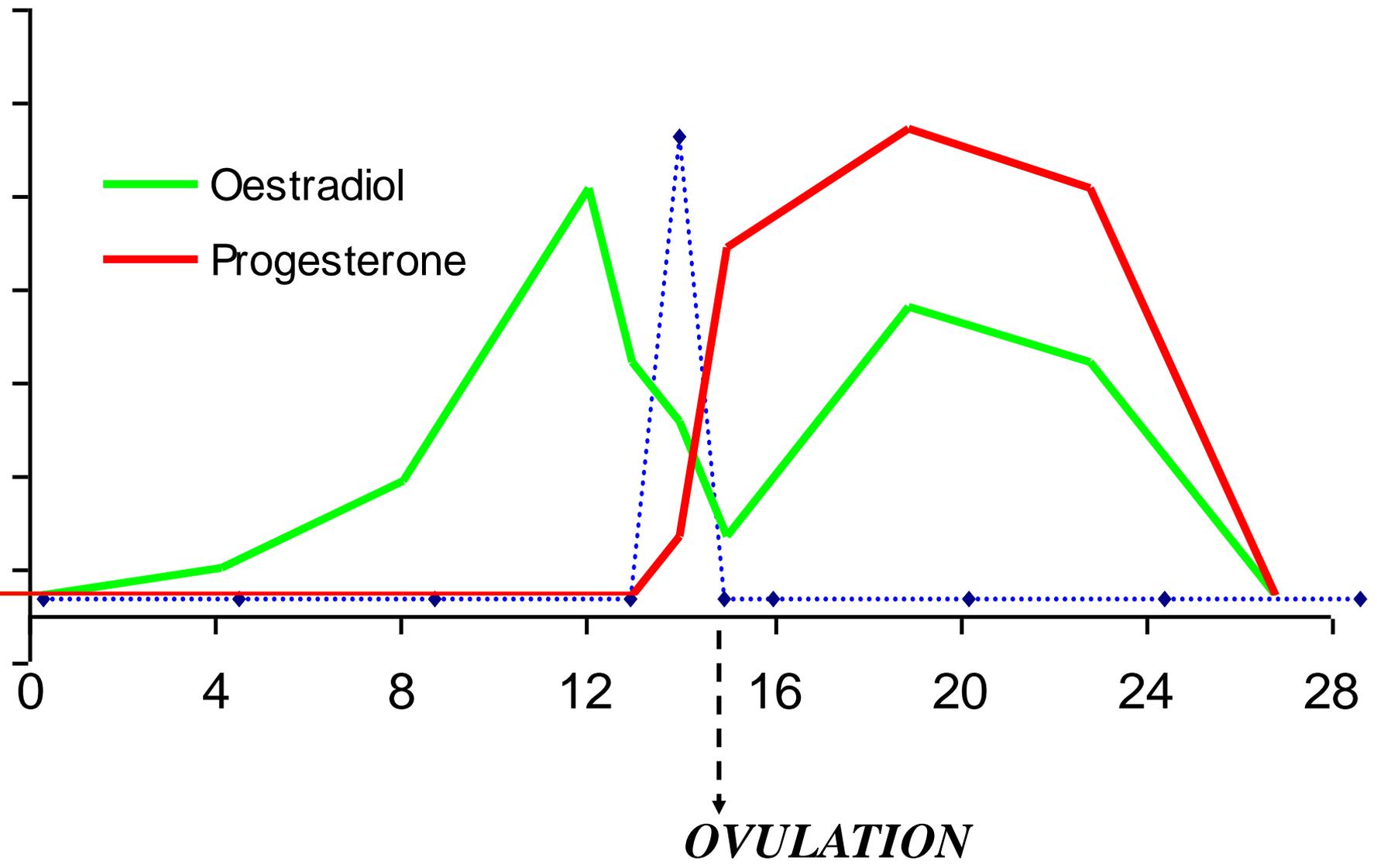
As CL degenerates...

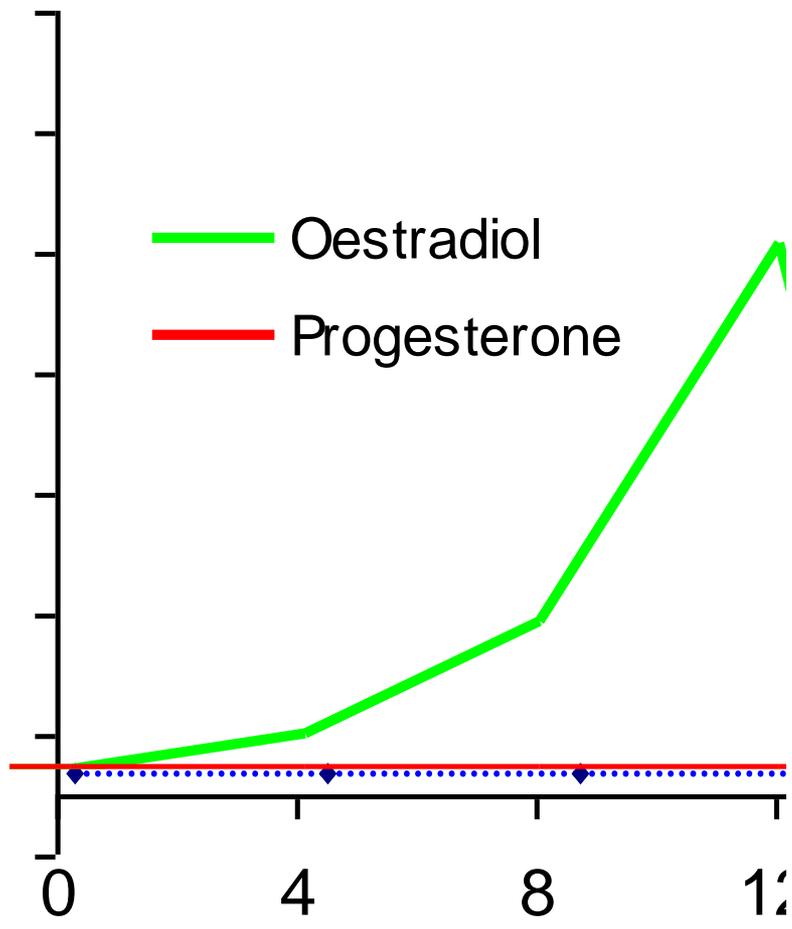
steroid negative feedback reduces ..

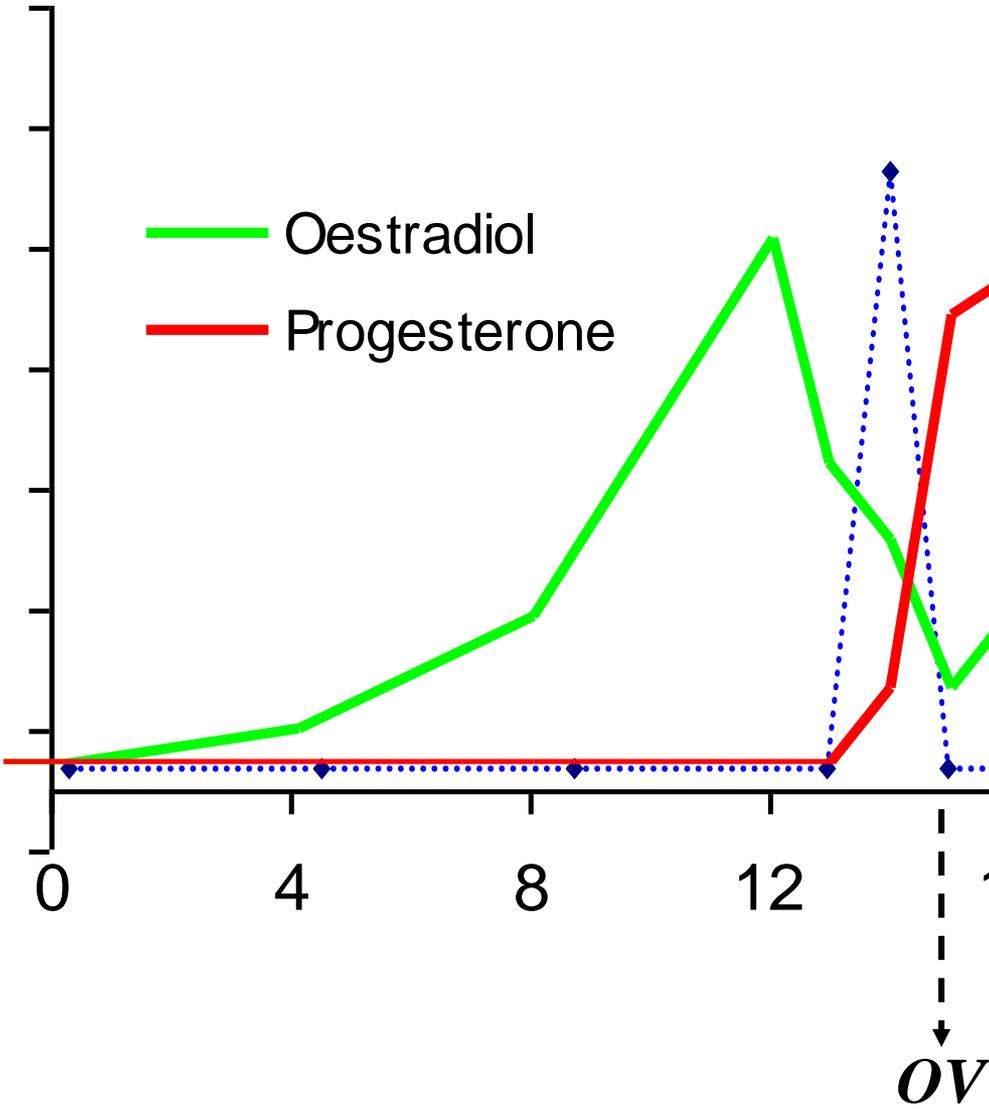
**New wave of
follicles stimulated
by rising FSH and**

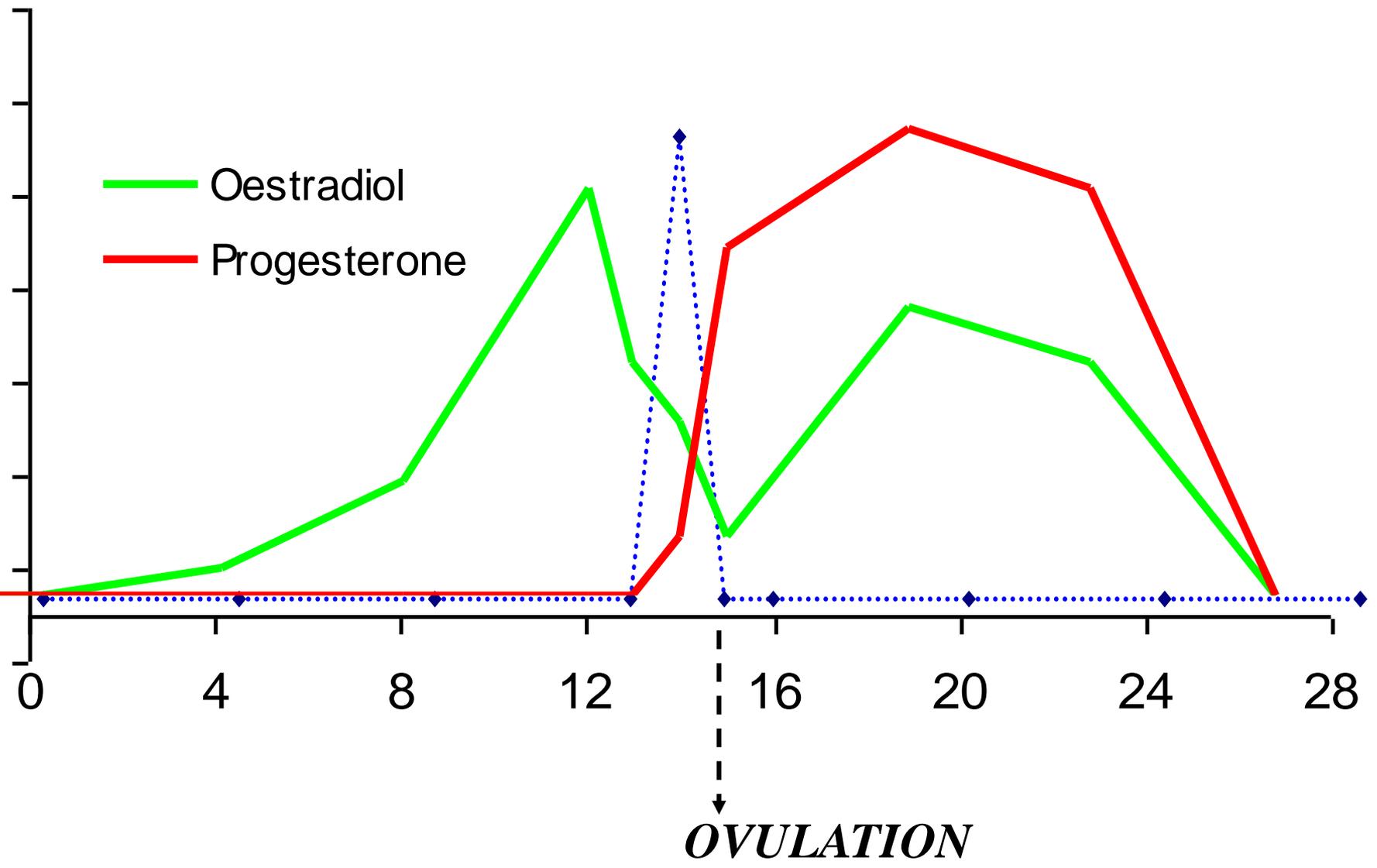
LH











Ovary: Details of Histology & Physiology

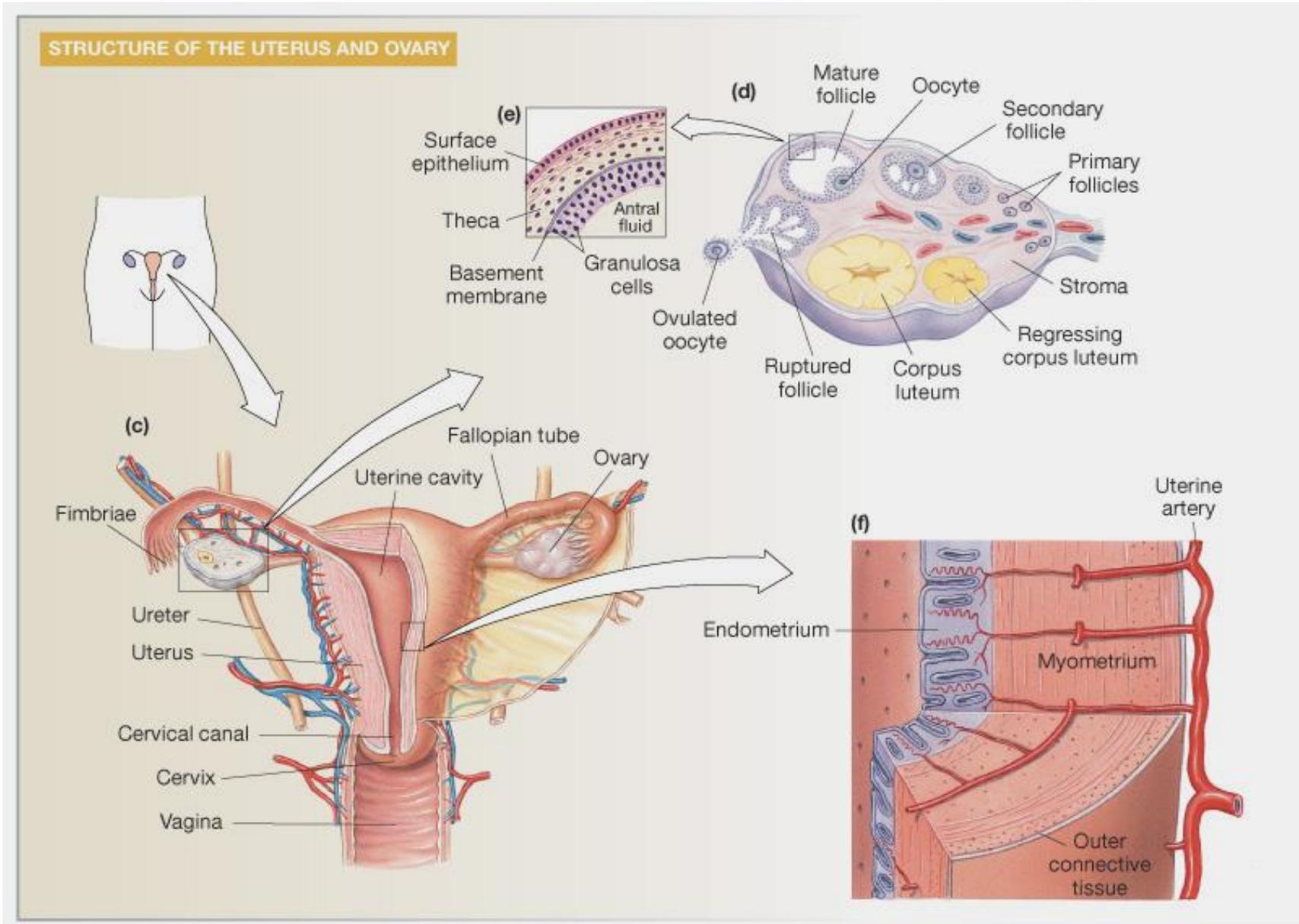


Figure 26-12d: ANATOMY SUMMARY: Female Reproduction

FUNZIONE ENDOCRINA DELL' OVAIO FOLLICOLO OVARICO - FUNZIONE

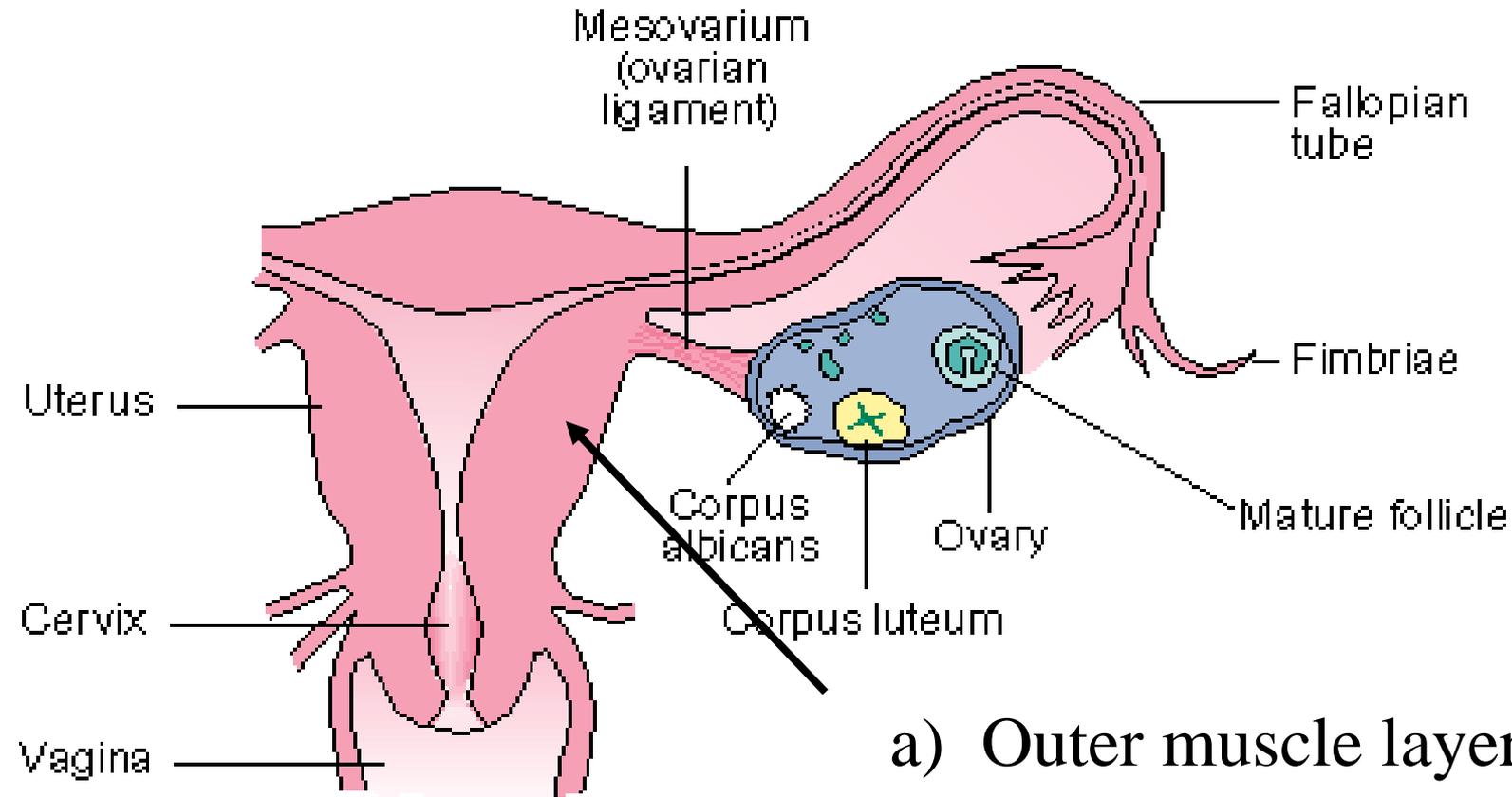
- **Proliferaazione delle cellule della granulosa**
- **Formazione della cavità antrale**
- **Differenziazione della teca interna ed esterna**
- **Ripresa della divisione meiotica** (iniziata nella vita prenatale e fermata a diplotene della metafase, riprende solo dopo il picco preovulatorio dell' LH)
- **Crescita e maturazione dell' ovocita con la formazion della membrana esterna** (zona pellucida)

FUNZIONE ENDOCRINA DELL' OVAIO

FOLLICOLO OVARICO - MORFOLOGIA

- Ovocita, circondato dalla zona pellucida
- Cellule della granulosa: steroidogenesi
- Fluido follicolare: fluidi proteici, ormoni
- Teca interna: all' esterno delle cellule della granulosa (m. Slaviansky), vascolarizzata
- Teca esterna: cell. muscolari e connettivali
- Entrambe le teche follicolari hanno una funzione steroidogenetica

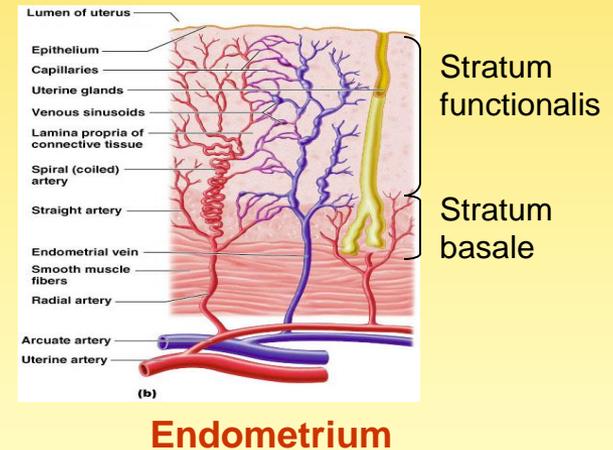
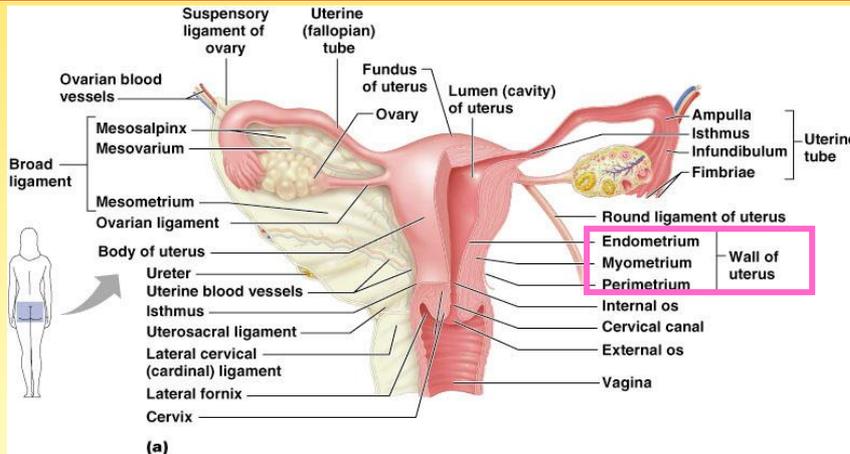
Other changes in the cycle



a) Outer muscle layer – the *myometrium*

b) Inner glandular mucosa – the *endometrium*

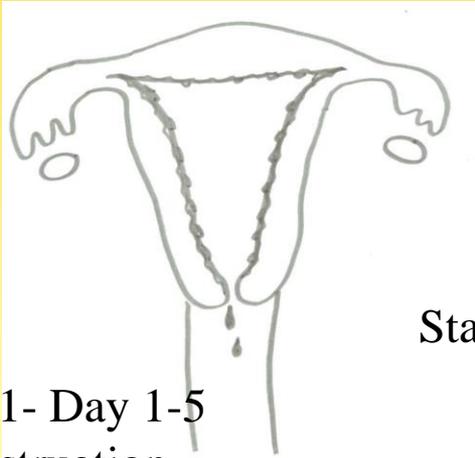
Uterine Wall



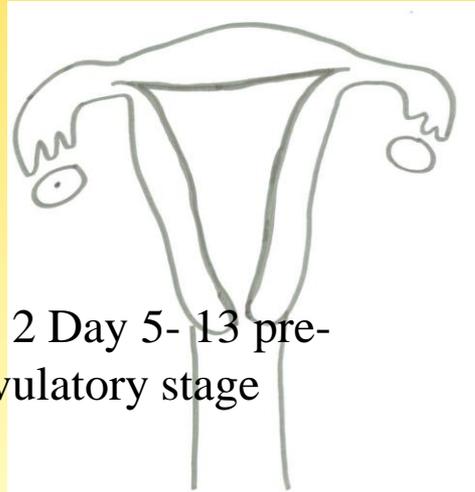
Composed of three layers

- **Perimetrium** – outermost serous layer; the visceral peritoneum
- **Myometrium** – middle layer; consists of interlacing layers of smooth muscles
- **Endometrium** – mucosal lining of the uterine cavity. It has numerous uterine glands and consists of
 - **Stratum functionalis**: It undergoes cyclic changes in response to ovarian hormones and is shed during menstruation
 - **Stratum basalis**: It forms a new functionalis layer after menstruation ends. It does not respond to ovarian hormones.

Changes in the Uterus:



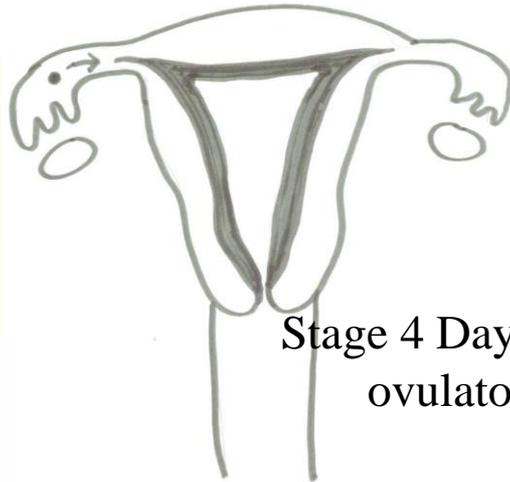
Stage 1- Day 1-5
menstruation



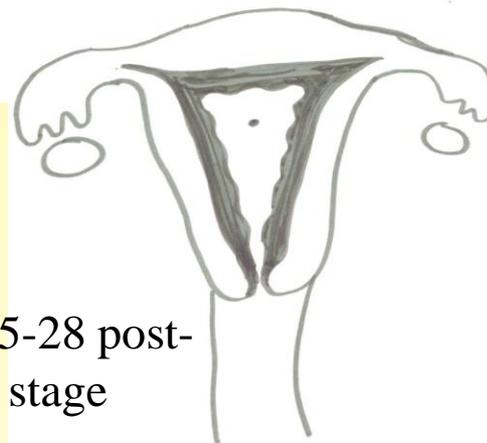
Stage 2 Day 5- 13 pre-
ovulatory stage



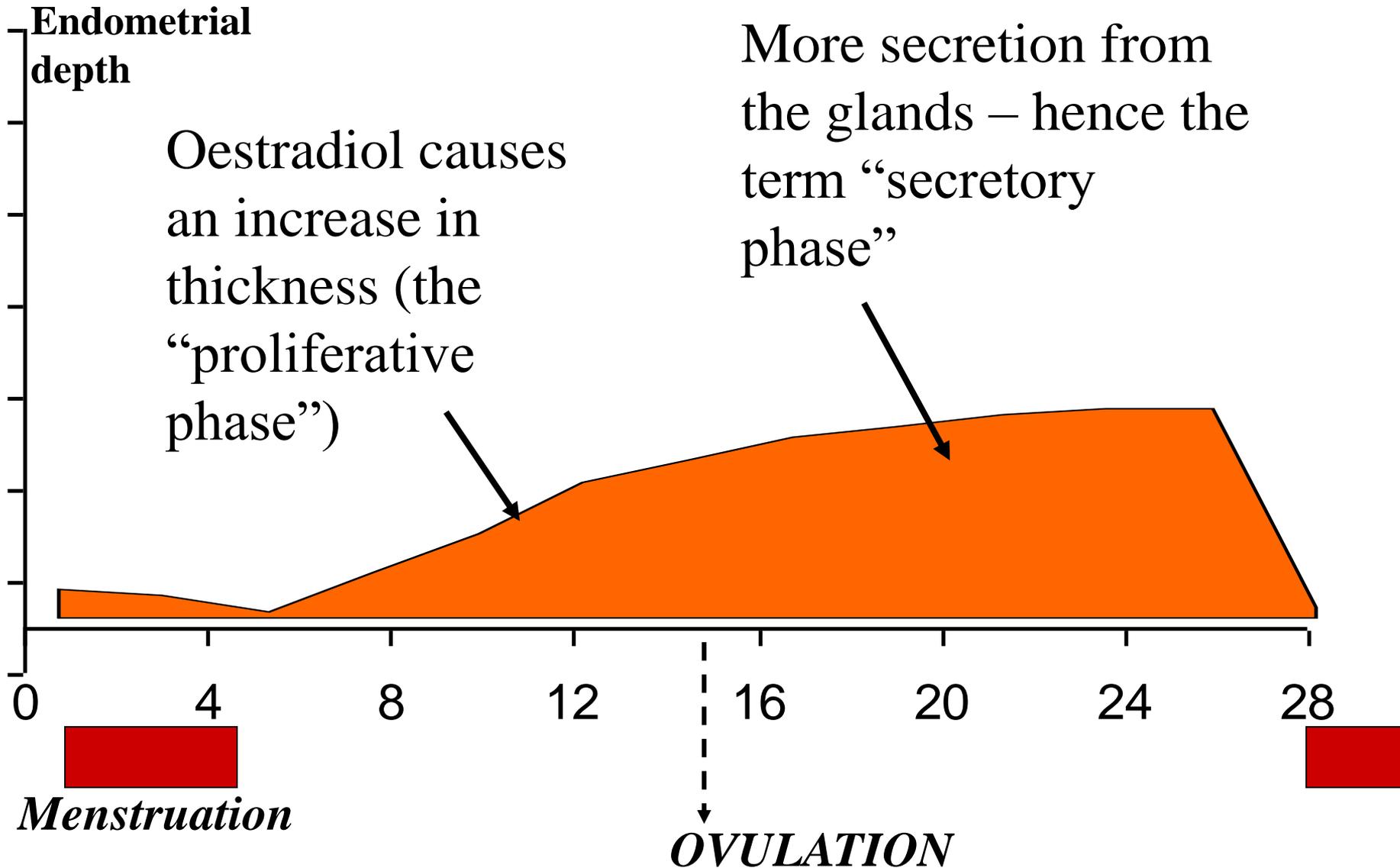
Stage 3 Day 14
Ovulation



Stage 4 Day 15-28 post-
ovulatory stage

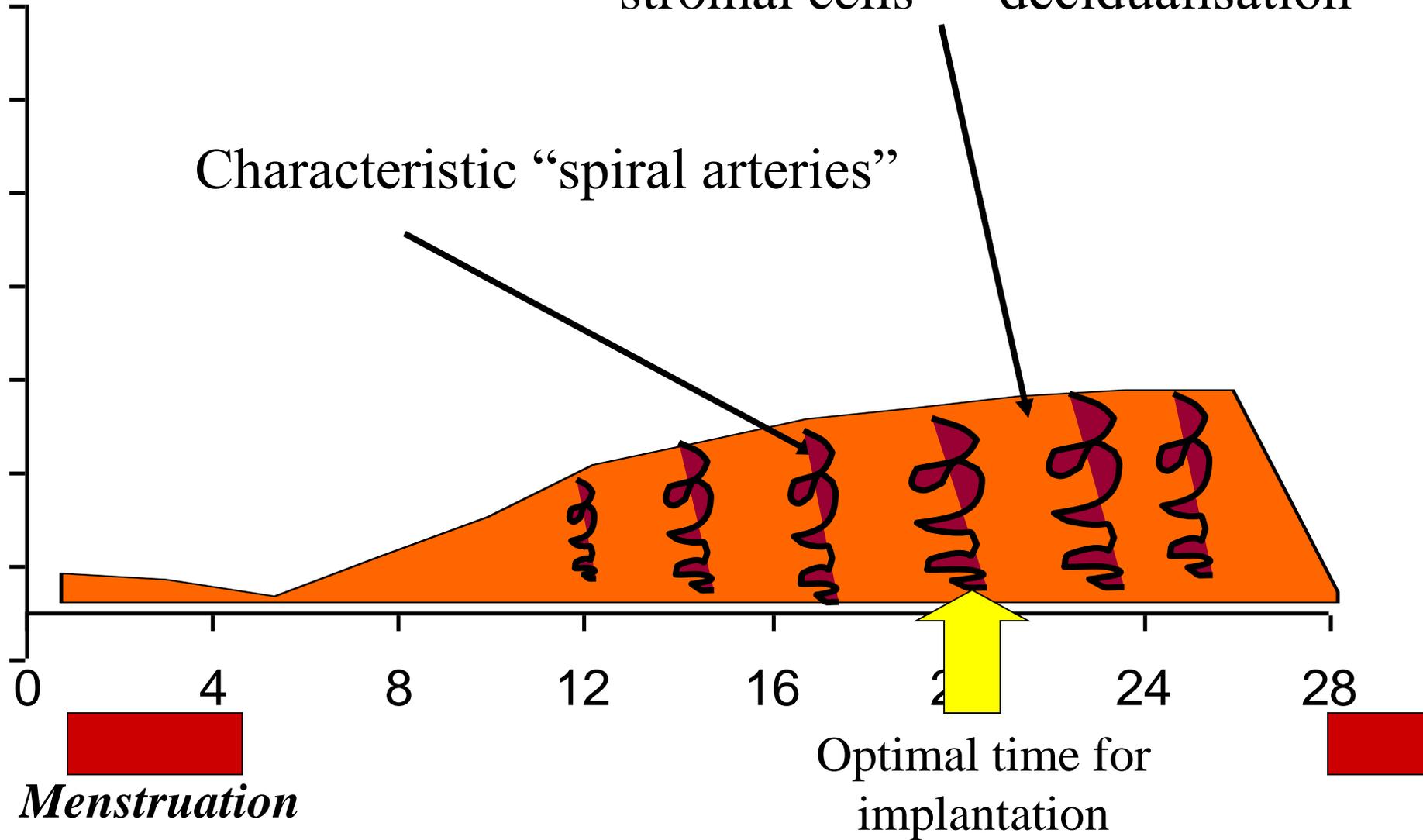


Uterine changes in the menstrual cycle.



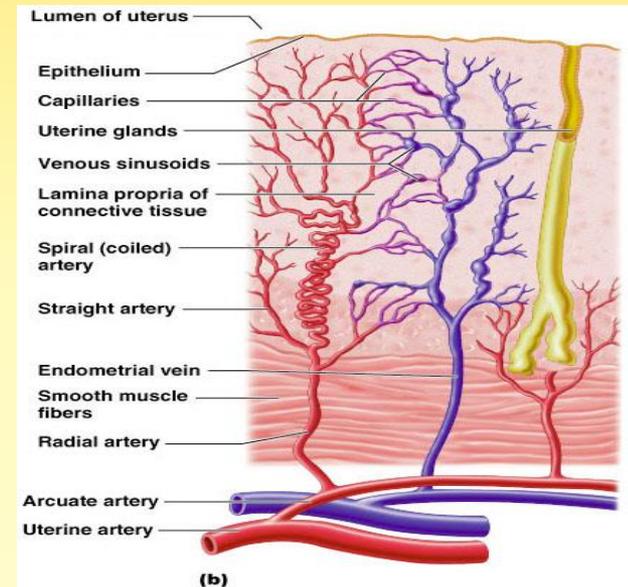
Terminal differentiation of stromal cells – “decidualisation”

Characteristic “spiral arteries”



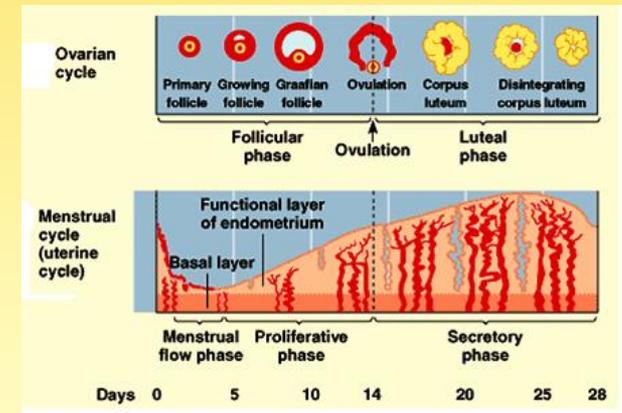
Uterine (Endometrial) Cycle

- Monthly cyclical changes in the endometrium of uterus for preparation of implantation (in the event of fertilization) and for menstruation (in the absence of fertilization) is called uterine cycle.
- The uterine endometrial cycle can be divided into three phases:
 - the **proliferative phase**,
 - the **secretory**,
 - the **menstrual phase**.



Uterine (Endometrial) Cycle

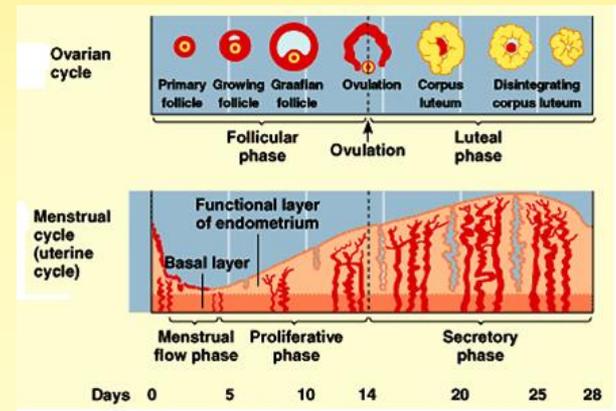
- **Proliferative Phase**
- The proliferative or follicular, phase, spans from the end of the menstruation until ovulation.
- Under the influence of increasing levels of estrogen secreted by ovarian follicles all elements of endometrium proliferate.
- The **raw surface of endometrium is again covered with epithelium** which proliferates out from the remains of the stems of uterine glands. The **stromal cells increase**



Uterine (Endometrial) Cycle

Proliferative Phase cont.

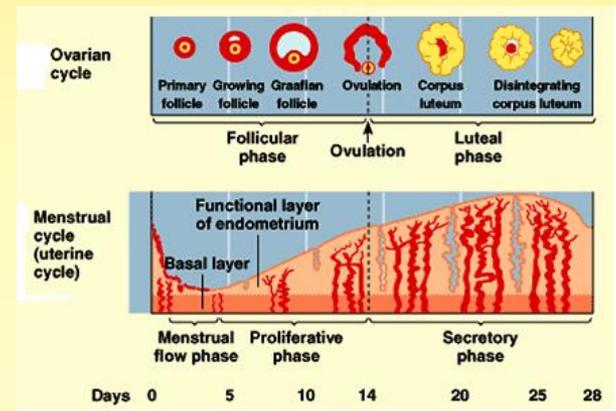
- Endometrial glands elongate with cells containing some glycogen. But it is not secreted during the follicular phase.
- Spiral arteries supplying blood also elongate. **Stratum functionalis** thus resumed again.



Uterine (Endometrial) Cycle

Secretory Phase

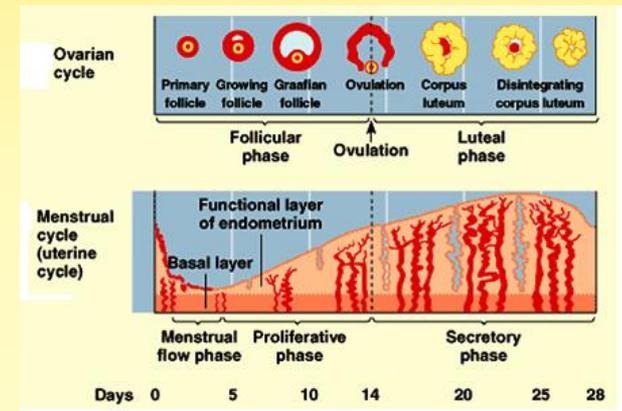
- The luteal, or secretory phase, begins at ovulation and lasts until the menstrual phase of the next cycle.
- At the beginning of the luteal phase, progesterone induces the **endometrial glands** to secrete glycogen, mucus, and other substances. These glands become tortuous and have large lumens due to increased secretory activity.



Uterine (Endometrial) Cycle

Secretory Phase cont.

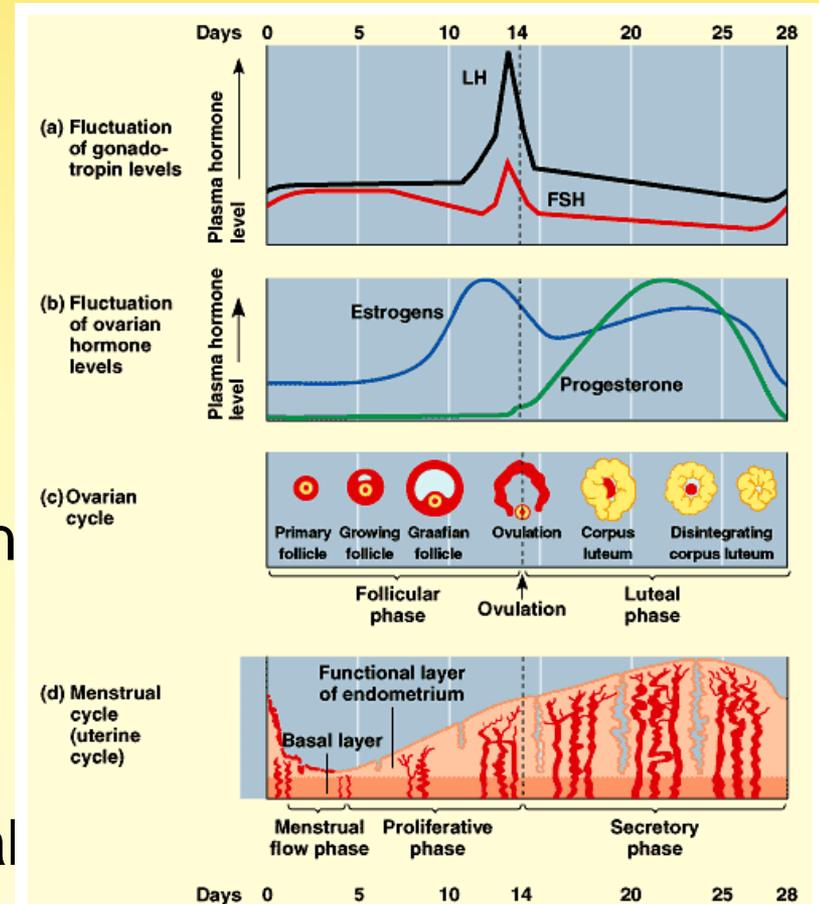
- The **spiral arteries** extend into the superficial layer of the endometrium.
- In the **absence of fertilization** by day 23 of the cycle, the corpus luteum begins to degenerate and consequently ovarian hormone levels decrease.



Uterine (Endometrial Cycle)

Secretory Phase cont.

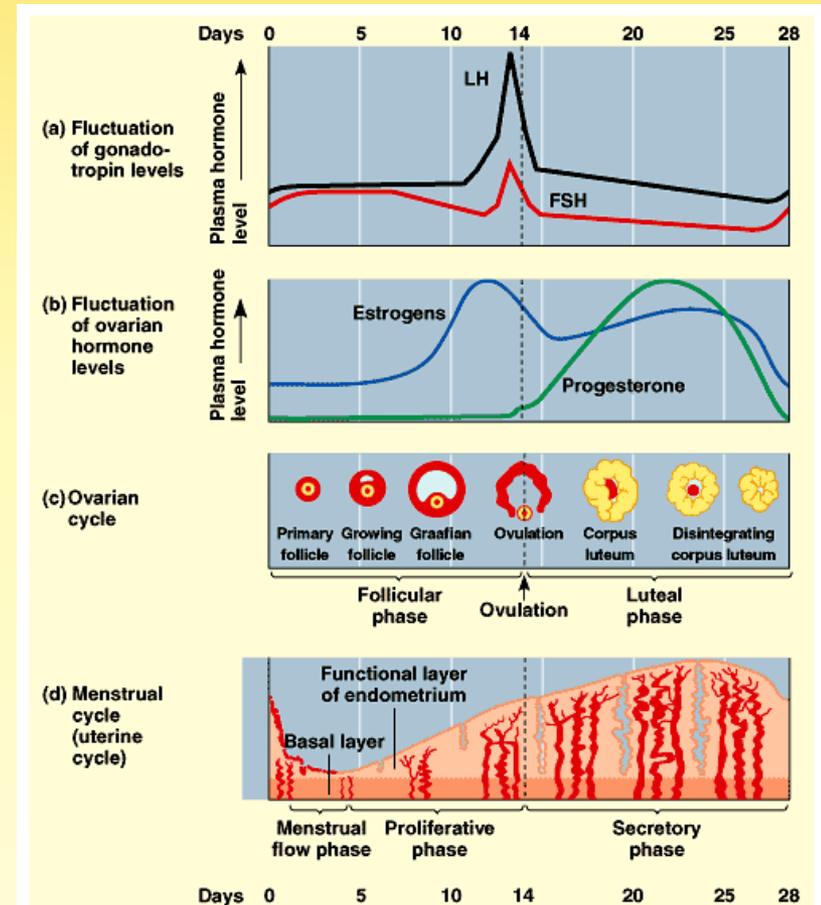
- As estrogen and progesterone levels decrease, the endometrium undergoes involution.
- Days 25-26 of the menstrual cycle, endothelin and thromboxin begin to mediate **vasoconstriction of the spiral arteries**. The resulting ischemia may cause some early menstrual cramps.



Uterine (Endometrial Cycle)

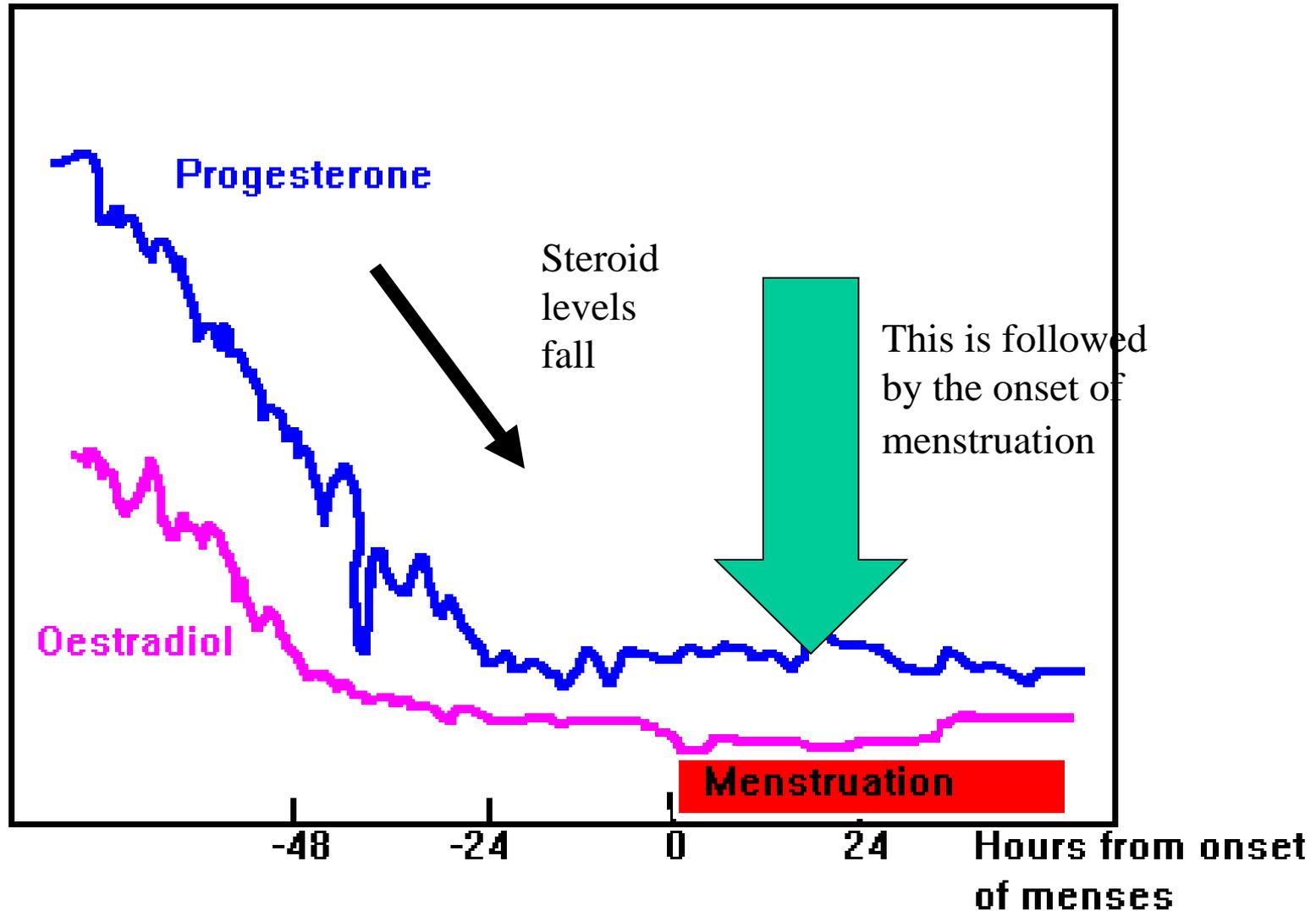
Secretory Phase cont.

- By day 28 of the menstrual cycle, intense vasoconstriction and subsequent ischemia cause mass apoptosis of the stratum functionalis.



What causes the onset of menstruation?

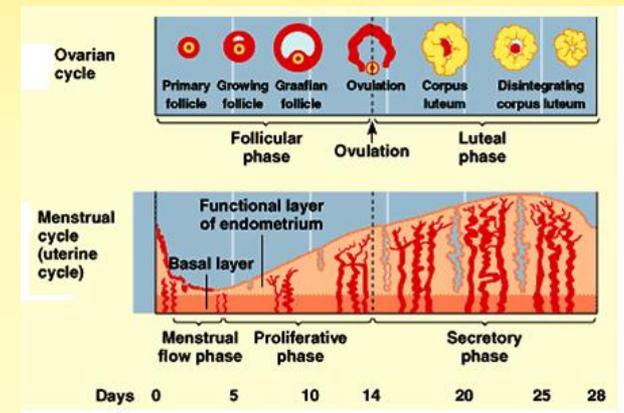
Plasma hormone level



Uterine (Endometrial) Cycle

Menstrual Phase

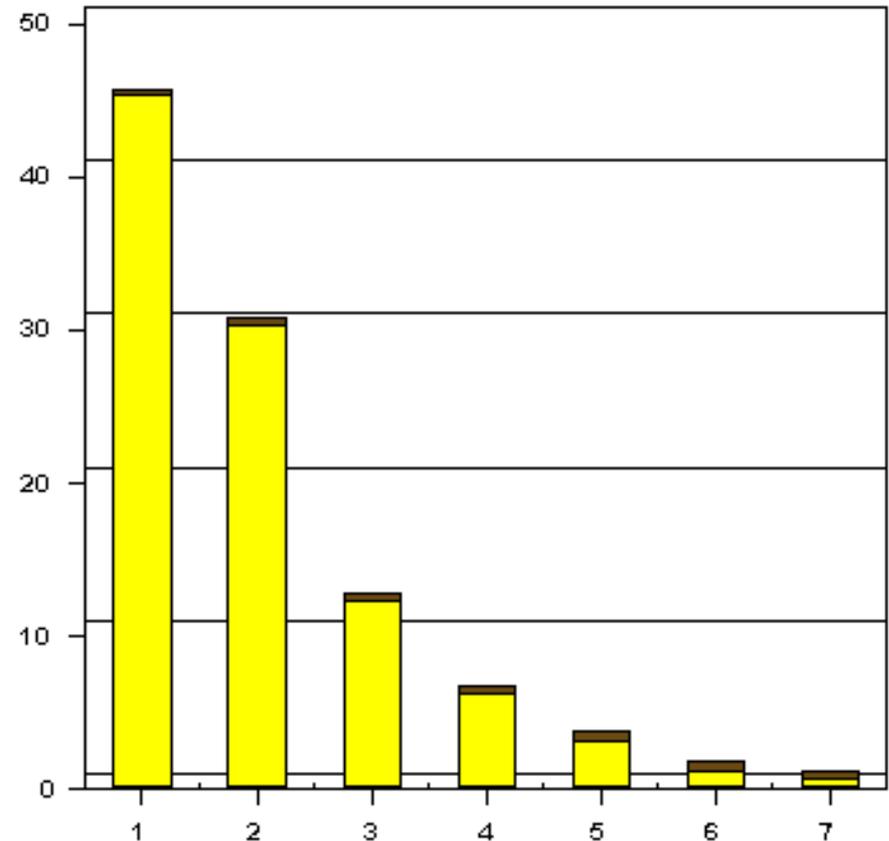
- The menstrual phase begins as the **spiral arteries rupture** secondary to ischemia, releasing blood into the uterus, and the apoptosed **endometrium is sloughed off**. It usually **lasts four days**. During this period, the **stratum functionalis is completely shed**.
- Arterial and venous blood, remnants of endometrial stroma and glands, leukocytes, and red blood cells are all present in the menstrual flow.



- 1. At end of the luteal phase, steroid production declines.**
- 2. Loss of oedema and gradual shrinking of endometrial tissue. The spiral arteries become more highly coiled**
- 3. Gradual reduction in blood flow to superficial layers – leading to ischaemic hypoxia and damage to the epithelial and stroma cells.**
- 4. 4-24 hours prior to menstrual bleeding, an intense constriction of spiral arteries occurs.**
- 5. Individual arteries re-open at different times, tearing and rupturing the ischaemic tissues.**
- 6. Bleeding into the cavity occurs via:**
 - 1. red cells diapedese between surface epithelial cells;**
 - 2. tears develop in the surface epithelium**
 - 3. pieces of weakened superficial endometrium crumble away**
- 7. About 50% of degenerating tissues is resorbed and 50% is lost as 'menstrual bleeding'.**

Time course of menstruation

% total
blood loss



Onset of menstruation is rapid.

Probably 95% of women have a total blood loss of less than 60 mls.

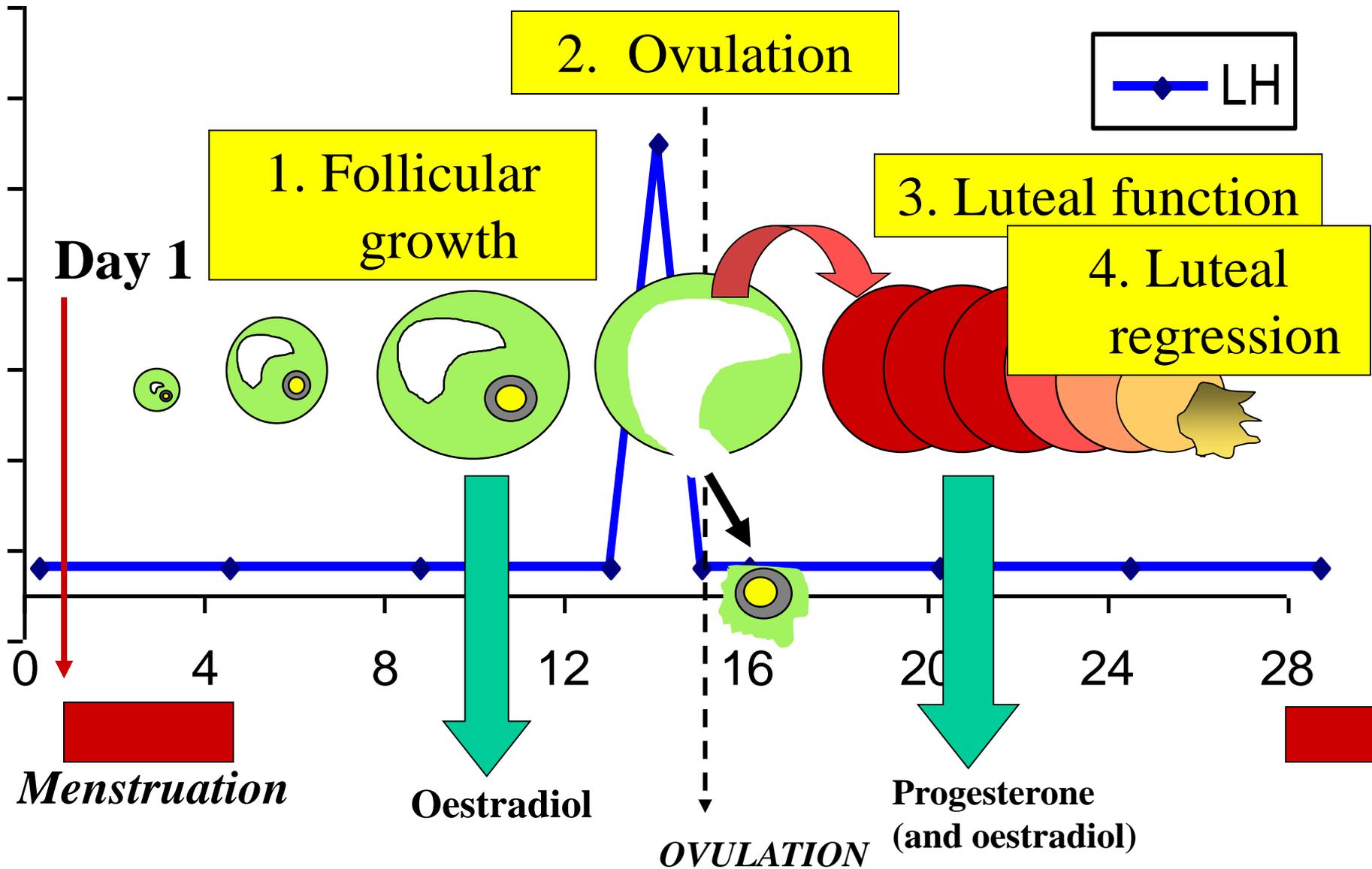
This blood loss can represent a significant loss of iron (leading to anaemia) – especially in women on marginal diets

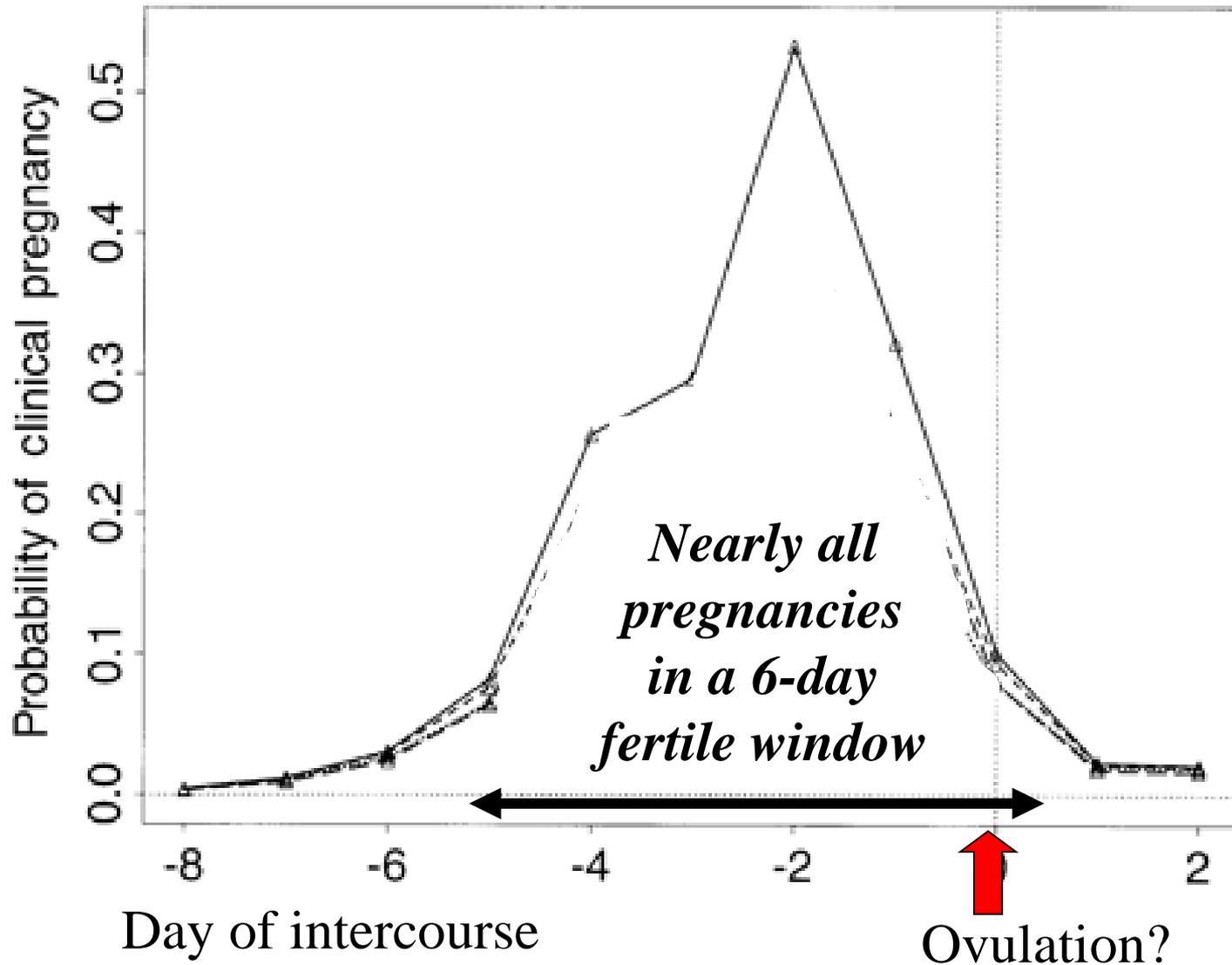
Menstruation - WHY?

In preparation for pregnancy, the human uterine stromal cells go through complex changes and the stromal cells terminal differentiate - “*Decidualization*”.

If implantation and pregnancy do not occur, this tissue is lost - and the uterus prepares itself again for another possible pregnancy.

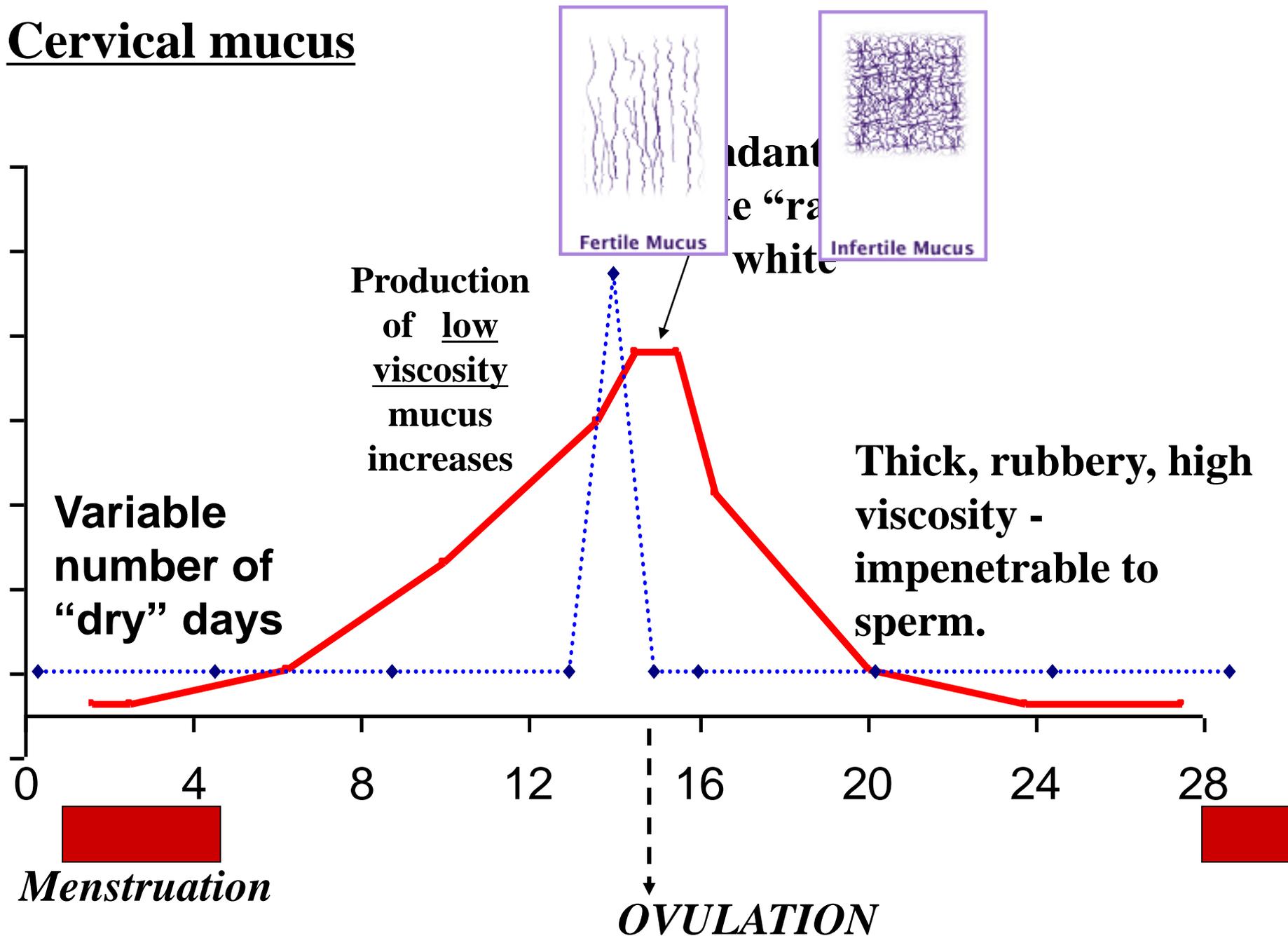
Key events in the ovarian cycle





Probability of clinical pregnancy following intercourse on a given day relative to ovulation (estimated from basal body temperature).

Cervical mucus



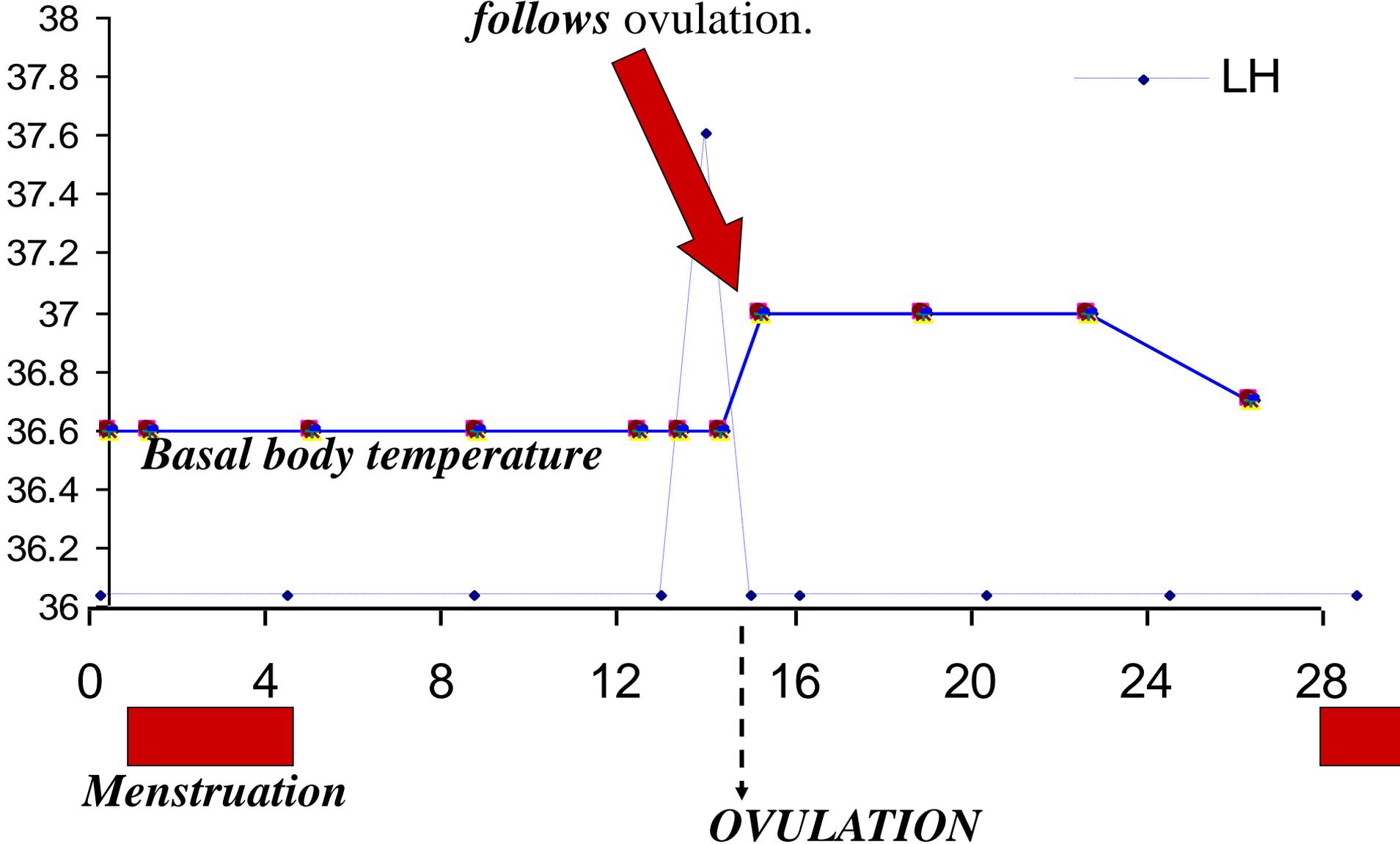
With increasing oestradiol:

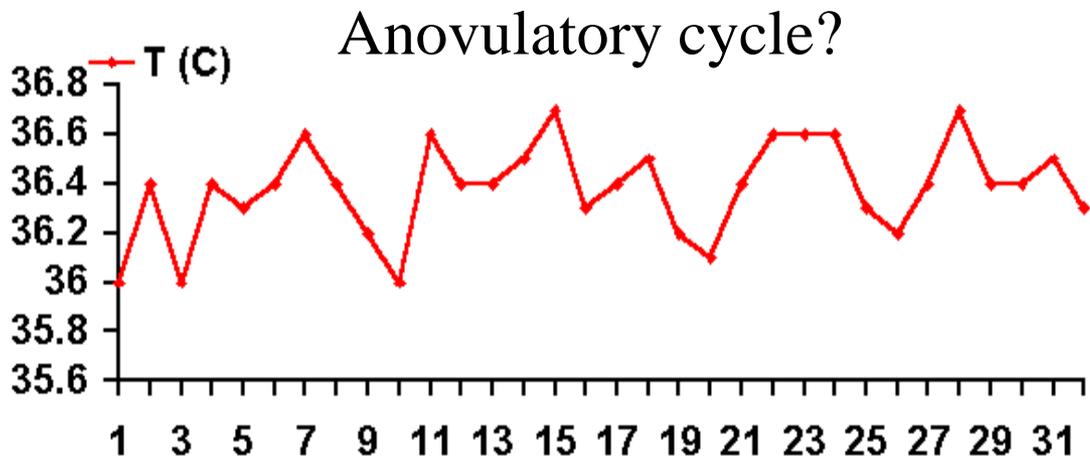
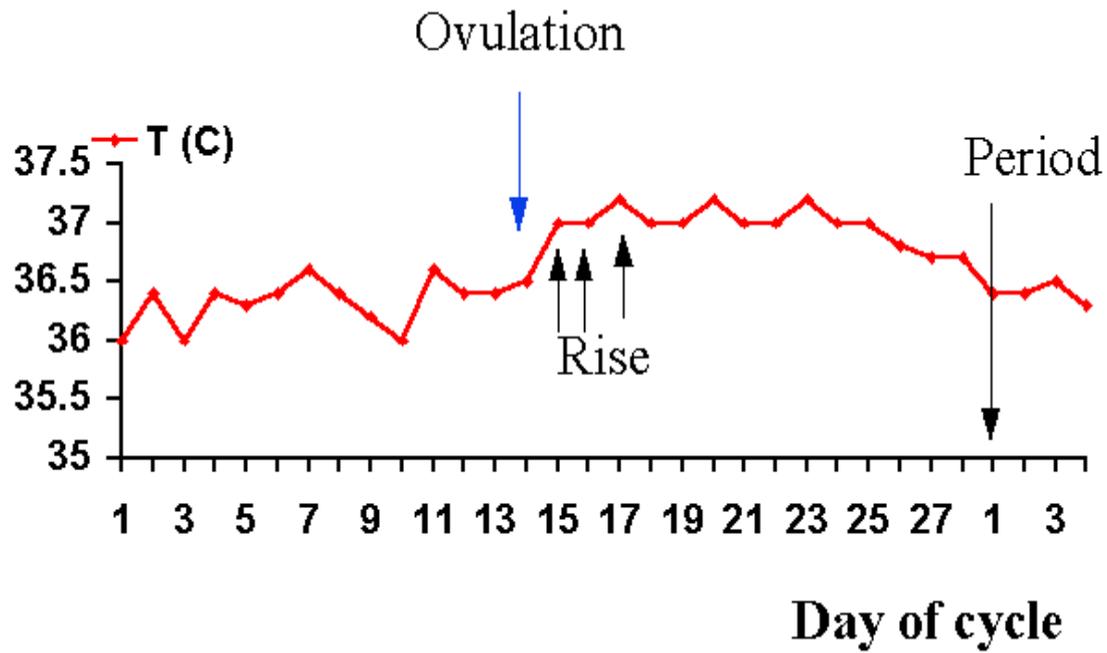
1. The mucus becomes more **abundant** - up to 30x more and its **water content increases**.
2. Its pH becomes alkaline.
3. Increased **elasticity** – ("**spinnbarkeit test**")
5. "Ferning pattern" caused by the interaction of high concentrations of salt and water with the glycoproteins in the mucus.

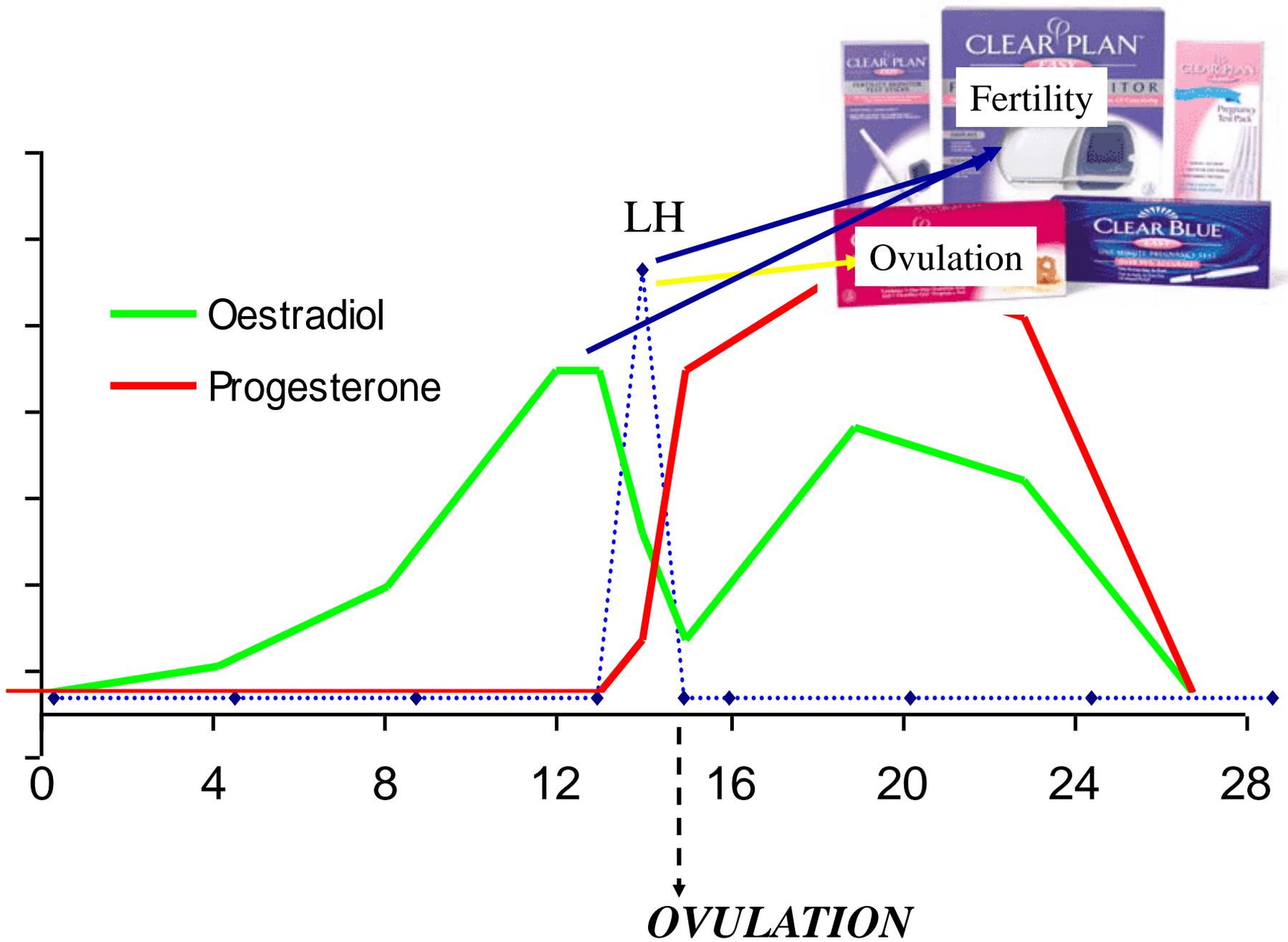


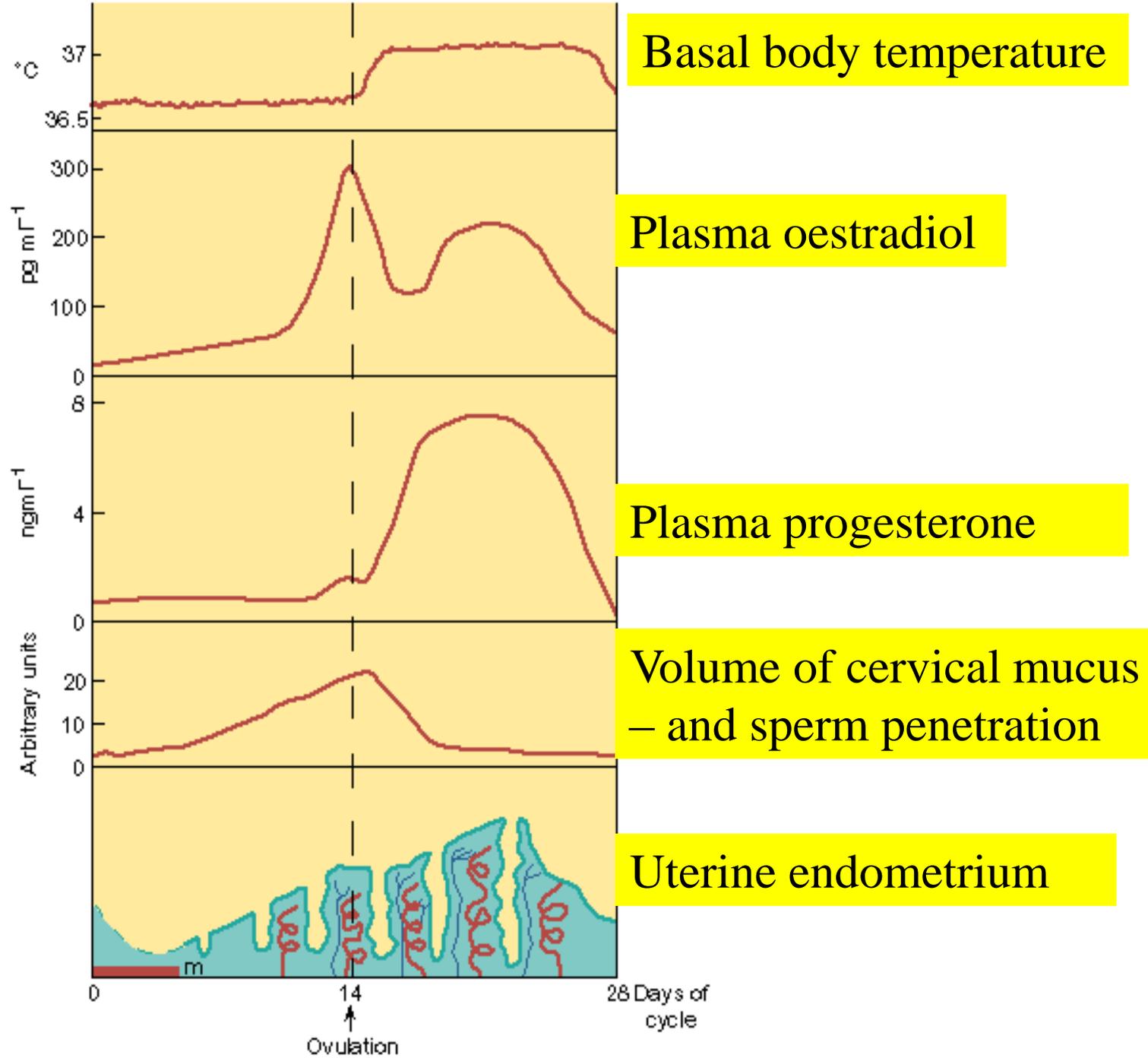
Characteristic fernlike pattern as the mucus dries on a glass slide.

A small (0.5 °C) rise
in BBT typically
follows ovulation.









There are a number of potential ways of trying to identify the “fertile” period...:

- a) **Calendar Method** - which is essentially based on the previous menstrual history.
- b) **Temperature method** - using a midcycle rise in body temperature as a sign when ovulation has occurred.
- c) **Cervical changes** - which can be detected by feeling the cervix and cervical mucus.
- d) **Hormonal methods** - using over-the-counter "kits" to assess urinary hormone levels.