5.4 Describe the regulation of female reproductive function

5.4.1 describe ovarian steroidogenesis as a compartmentalized process

General Information

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- ovaries have two key functions:
  (i) produce oocytes
  (ii) produce reproductive hormones (eg: **estradiol**, **progesterone**)

Remember: • the hormones a cell can produce depends on the enzymes it has
• steroids are lipids – can easily traverse PMs

CHOLESTEROL

↓

progesterone

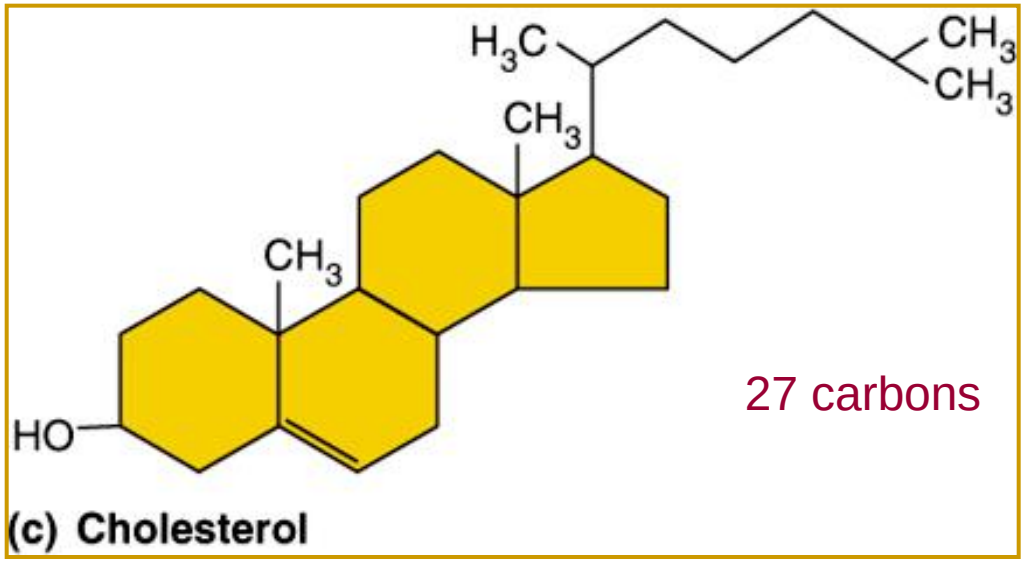
androstenedione

↓

testosterone

↓

estradiol



27 carbons

5.4.2 describe the hypothalamic & pituitary regulation of steroid hormone production in the female

- there are 3 types of steroid hormones produced in the ovarian follicle

A. Progestins (eg: progesterone - all have 21 carbons)

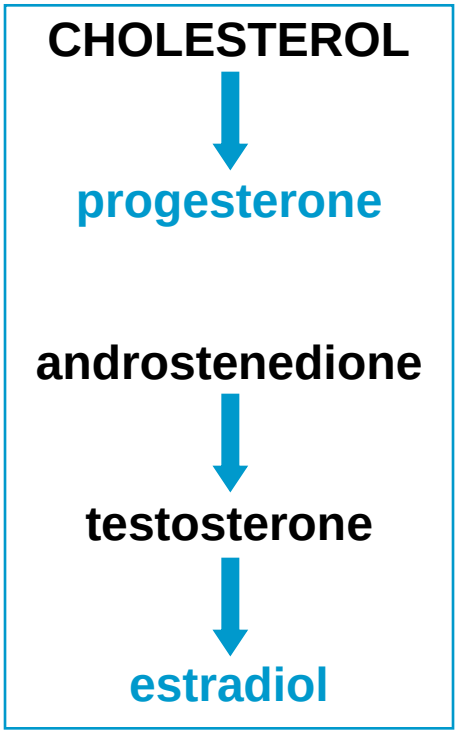
- produced by all major ovarian cell types: follicular **granulosa** cells, **theca** cells, **corpus luteum**
- most important as a product of the corpus luteum - during luteal phase of menstrual cycle & for maintenance of pregnancy

B. Androgens (eg: testosterone - all have 19 carbons)

- most important as a precursor for synthesis of estradiol in developing follicle
- synthesized by follicular theca cells and by corpus luteum
- too much testosterone is associated with follicular atresia

C. Estrogens (eg: estradiol - all have 18 carbons)

- synthesized by follicular granulosa cells and corpus luteum
- essential for stimulation of follicular development, onset of puberty, etc.



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Hypothalamus

↓

Anterior Pituitary

↓

Ovary

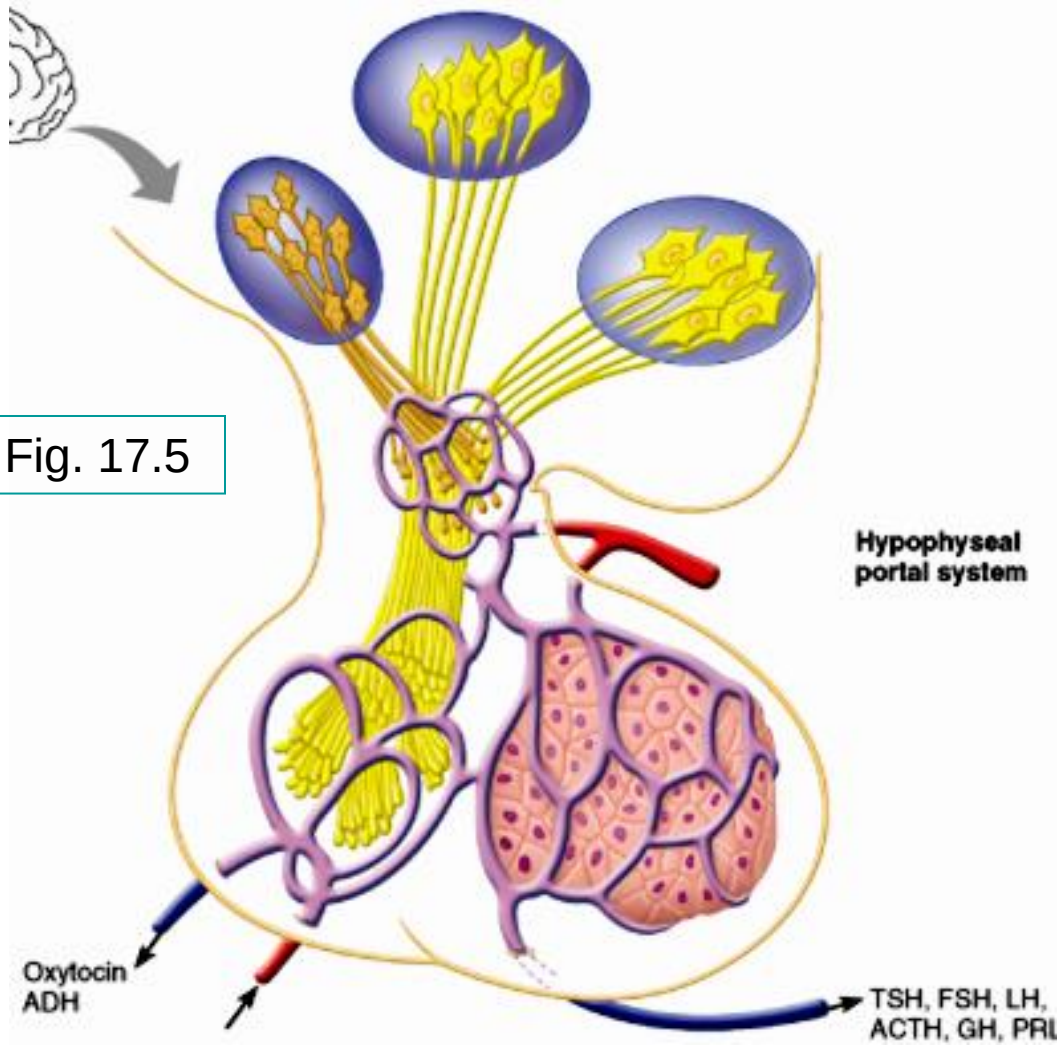


Fig. 17.5

Hypothalamic-Pituitary Axis:

Anterior Pituitary Hormones:

(i) FSH

- stimulates ovarian follicles to grow & produce estradiol

(ii) LH

- stimulates testosterone production by theca cells
- stimulates ovulation, secretion of steroid hormones by corpus luteum

Hypothalamus:

- the secretion of both FSH & LH is stimulated by **GnRH**

5.4.3 describe ovarian follicular development & its hormonal regulation

- What is the goal of each menstrual cycle?

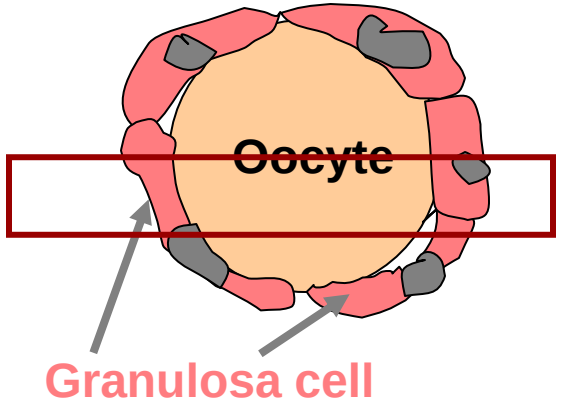
A. Primordial follicle:

starting point - oocyte surrounded by single layer of flattened granulosa cells

- oocyte (primary oocyte) **arrested** at prophase of meiosis I
- by 6 mo postpartum, ovary has full complement of primordial follicles
- ~2 million at birth; gradual loss (degeneration); ~400,000 remain by puberty

Primordial Follicle = oocyte + single layer of flattened granulosa cells

Initiation of development of primordial follicles does NOT require gonadotropic stimulation - some follicles can and do begin developing at any time



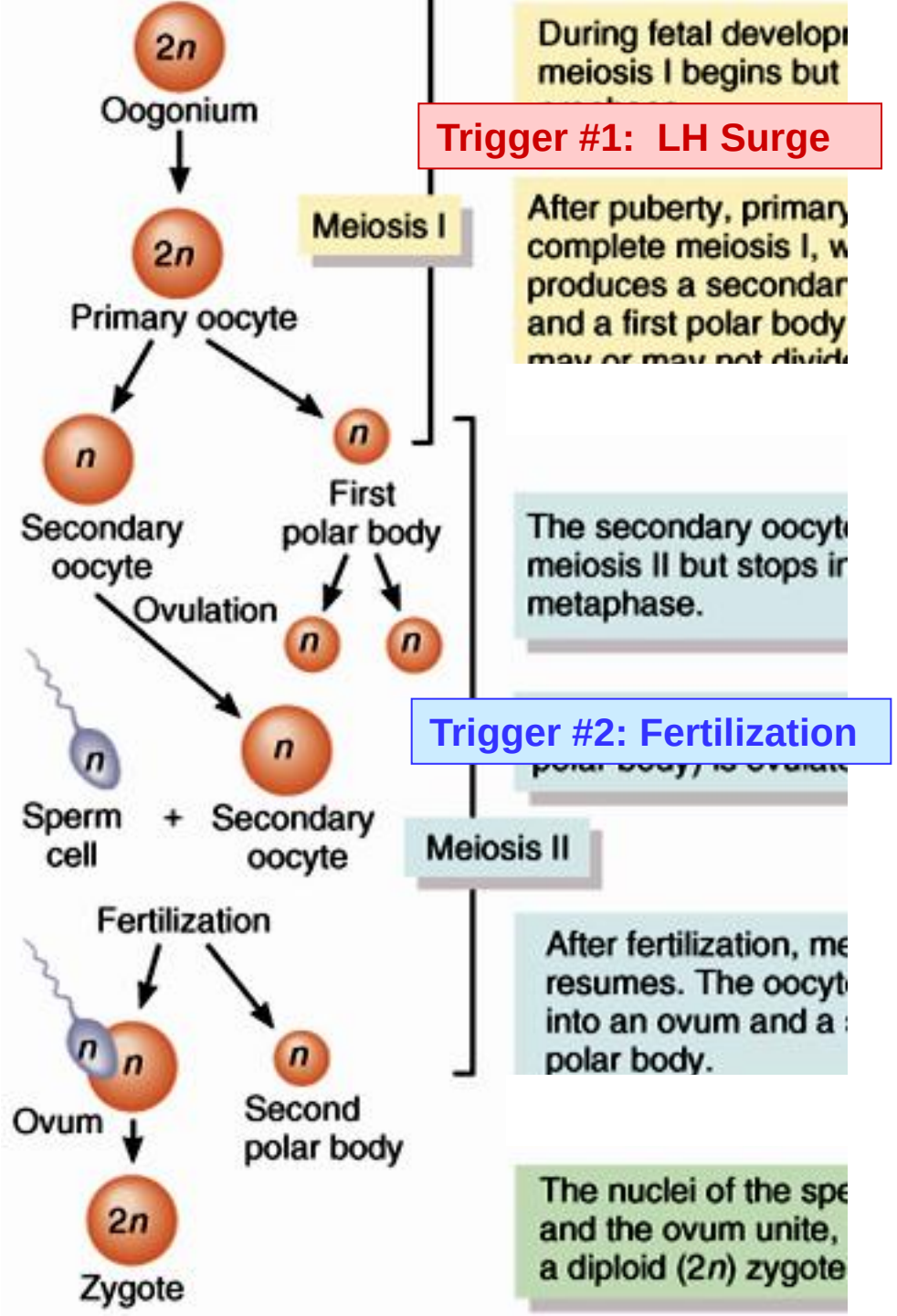
oogonia to primary oocytes accomplished by birth

At what stage are oocytes arrested? What would they look like under the microscope?

What triggers the resumption of meiosis?

What is the fate of most primary oocytes??

What is the fate of most oocytes in which resumption of meiosis was initiated by trigger #1?



B. From Primordial to Primary Follicle:

- **gonadotropin-independent**

  (i) oocyte increases in size & acquires a **zona pellucida**

  (ii) **granulosa** cells start to divide & form several layers outside oocyte

  (iii) outside bm ovarian interstitial cells closest to growing follicle differentiate to form **theca** cells

- now called a primary follicle - **continued maturation of this follicle requires what??**

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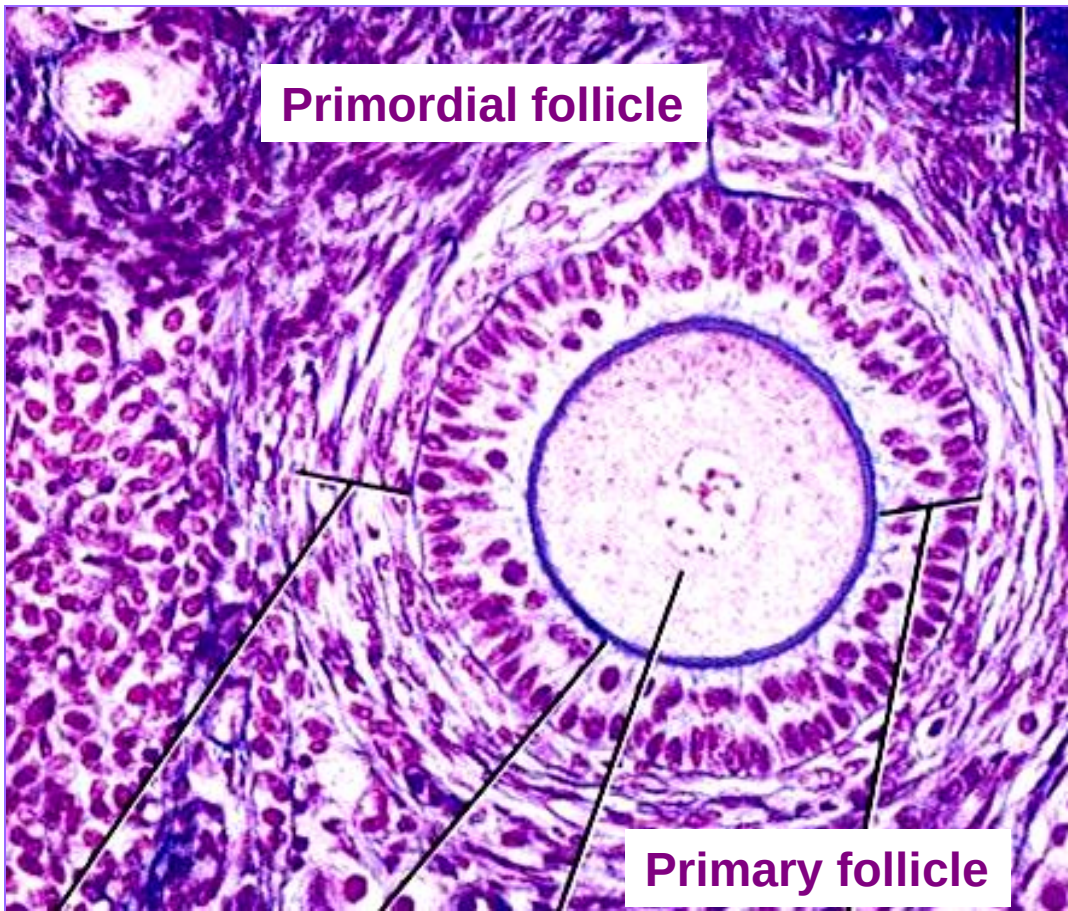
T&G



C. Secondary (Antral) Follicle:

*What is an **antrum**? Why is it important to have an **antrum** in a maturing follicle?*

- basement membrane divides follicle into 2 compartments:

(i) inner **granulosa cell** compartment

> nonvascularized

> FSH-responsive:

- granulosa cell proliferation (E)
- granulosa cell E production
- more FSH receptors

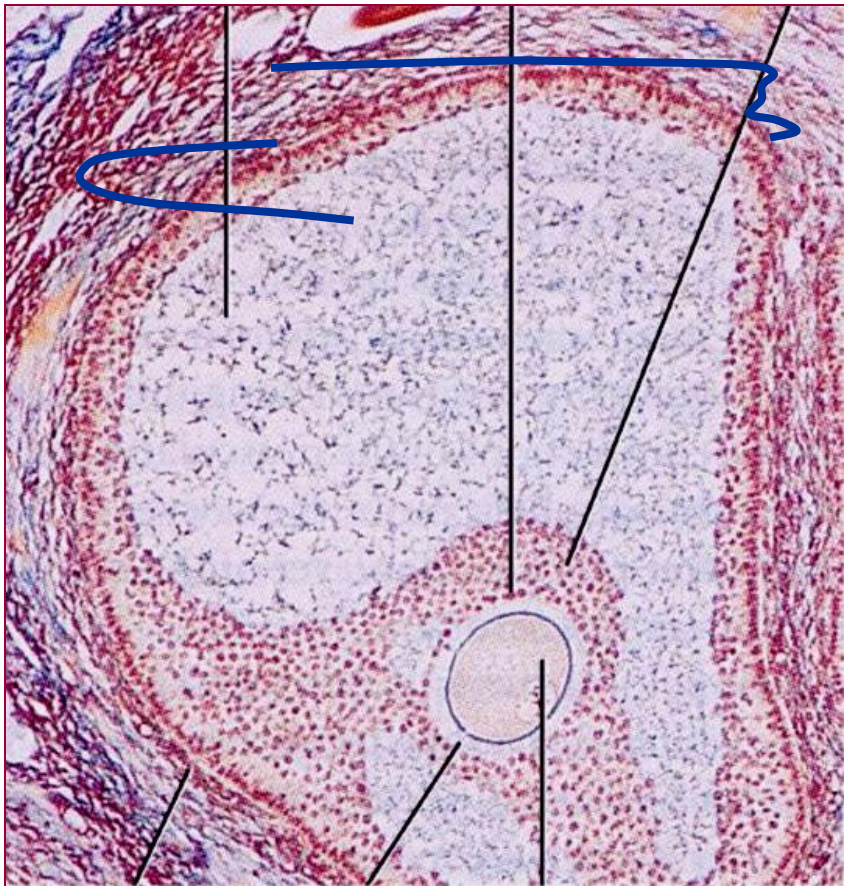
(ii) outer **theca cell** compartment

> vascularized

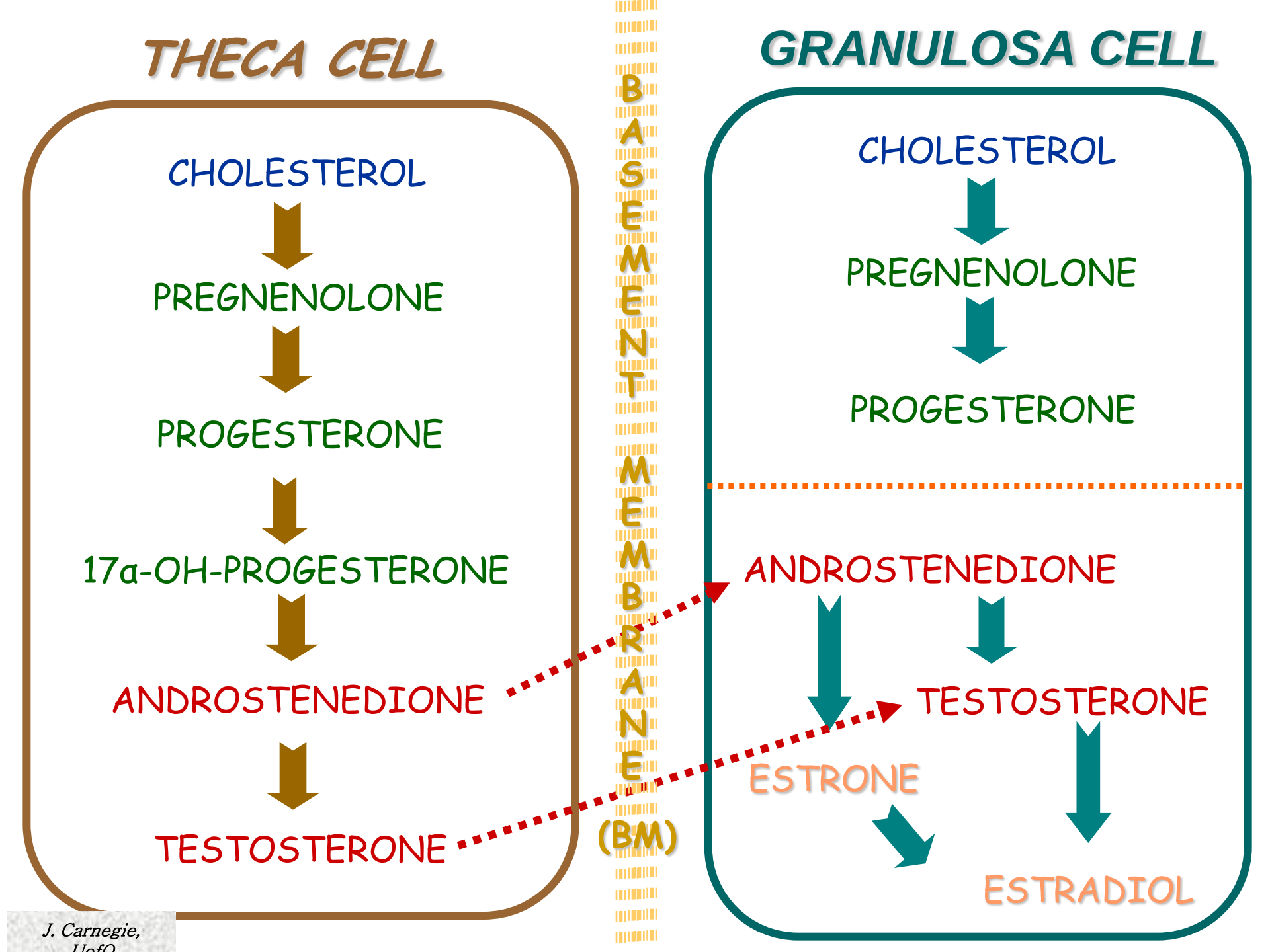
> LH-responsive:

- T production for use by granulosa cells

Secondary follicle



T&G



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Timing is Everything!

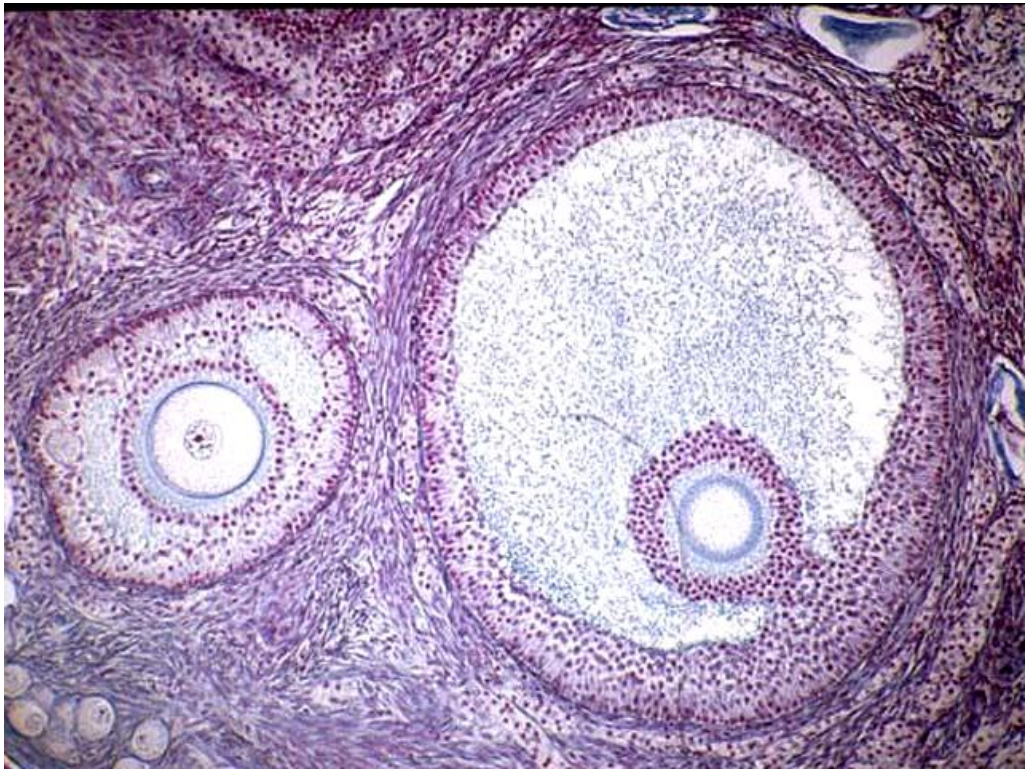
- if development coincides with **rising FSH levels** at beginning of cycle → development will be supported - otherwise: ***atresia!!***
- for one follicle to become **dominant**, must convert potentially androgenic environment to estrogenic environment - otherwise: ***atresia!!***

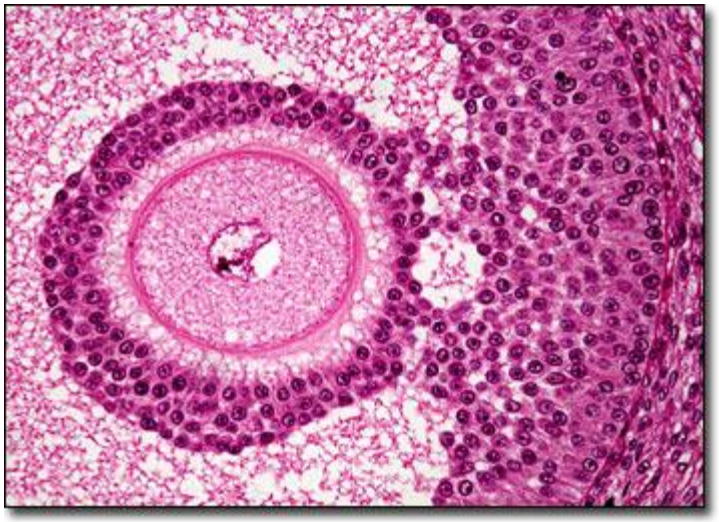
D. Emerging dominant follicle becomes the preovulatory follicle

E levels continue to rise - FSH switches to **inducing receptors for LH**

➢ LH stimulates further E & P production

stage is set for **LH surge** to trigger ovulation





http://virtual.yosemite.cc.ca.us/randerson/Lynn's%20Bioslides/98.jpg

5.4.4 describe ovulation & its regulation

LH stimulates:

1. resumption of meiosis - extrusion of PB#1
2. P production by granulosa cells
3. increase in antral fluid volume
4. release of hydrolytic enzymes

minor FSH surge:

ensures sufficient LH receptors for luteal phase

stimulates synthesis of **hyaluronic acid** - important in **cumulus expansion**

what are cumulus cells?

what is a COC?

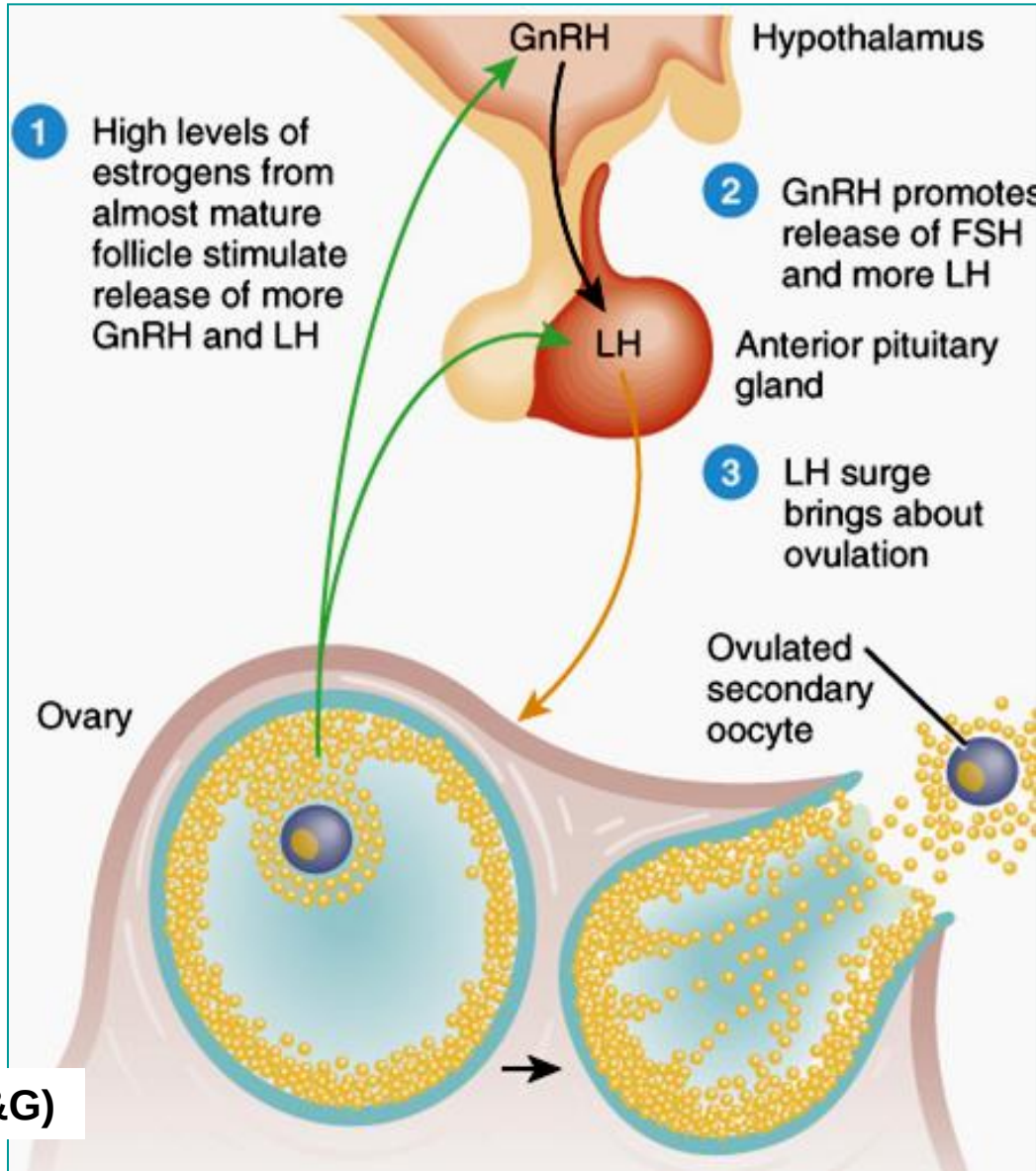
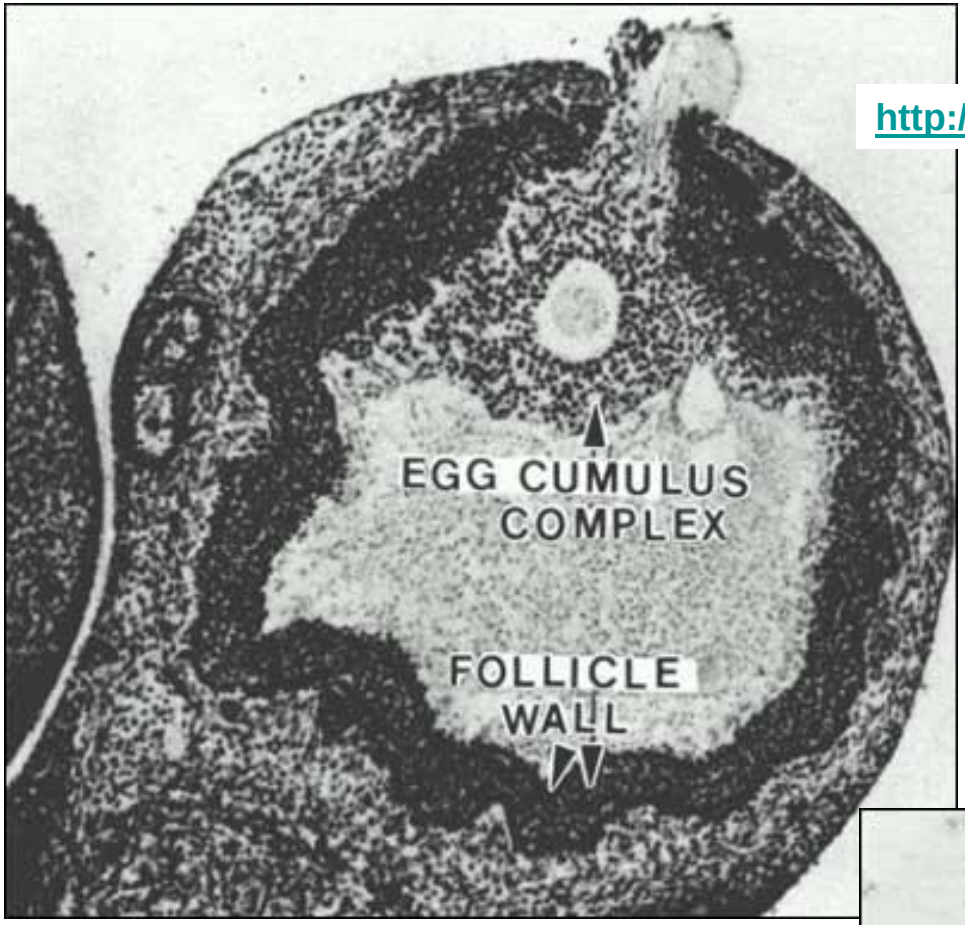
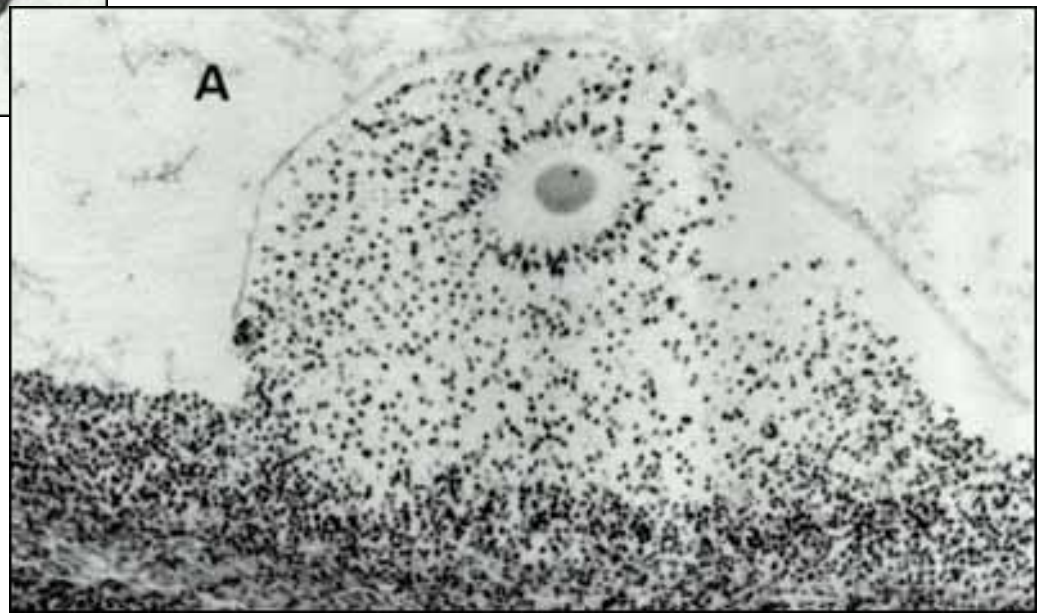


Fig.28.28 (T&G)



http://www.endotext.org/female/female1/female1_4.htm

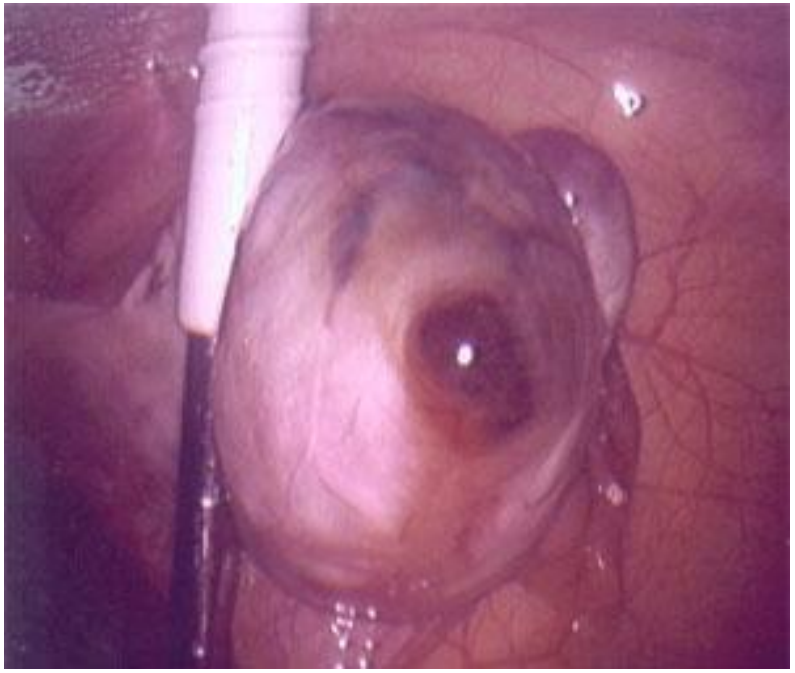


5.4.5 describe the corpus luteum as a transient endocrine structure

corpus luteum = yellow body

capillaries bring cholesterol to follicle

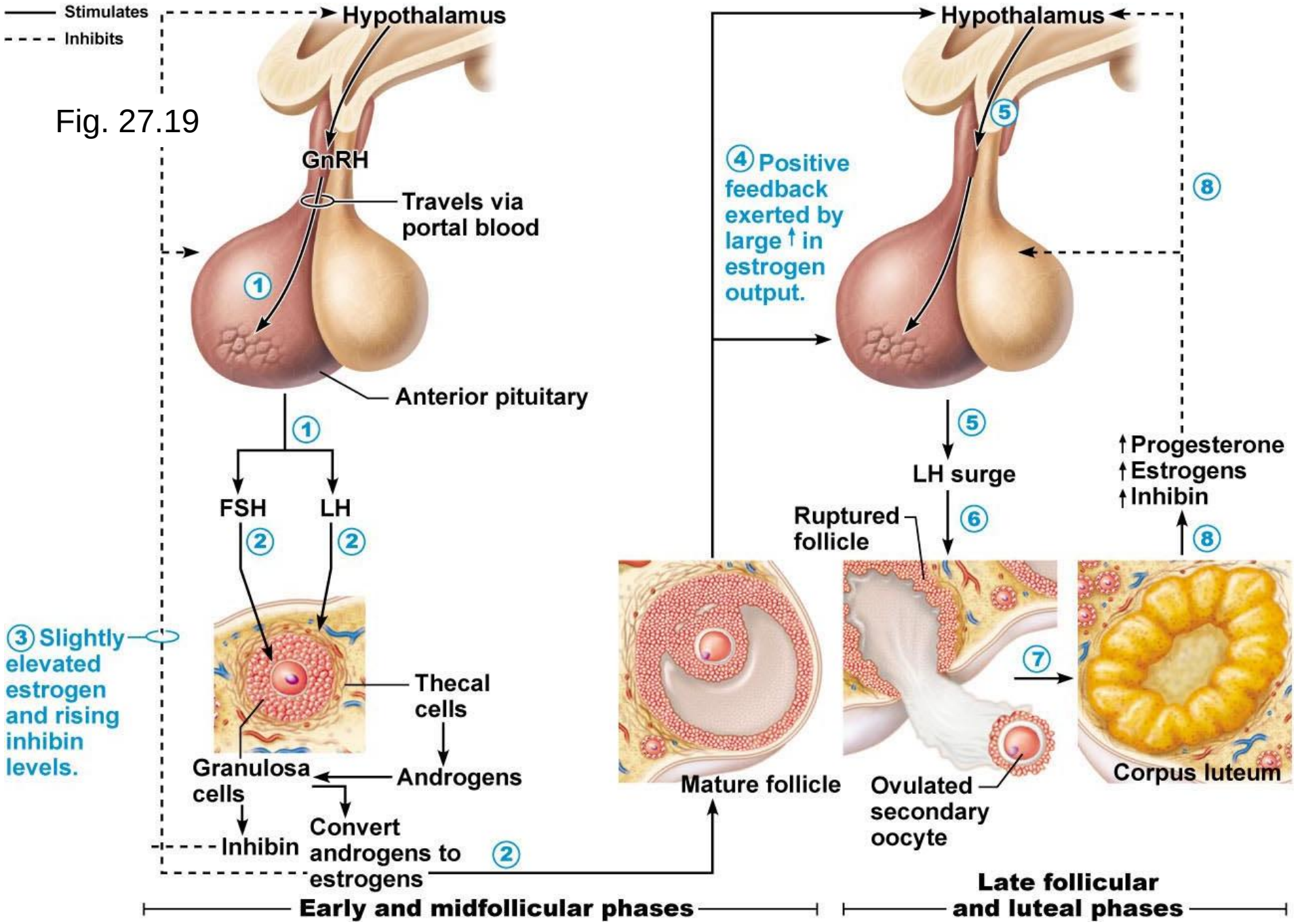
home.cfl.rr.com/dahmd/ images/corpusluteum.jpg

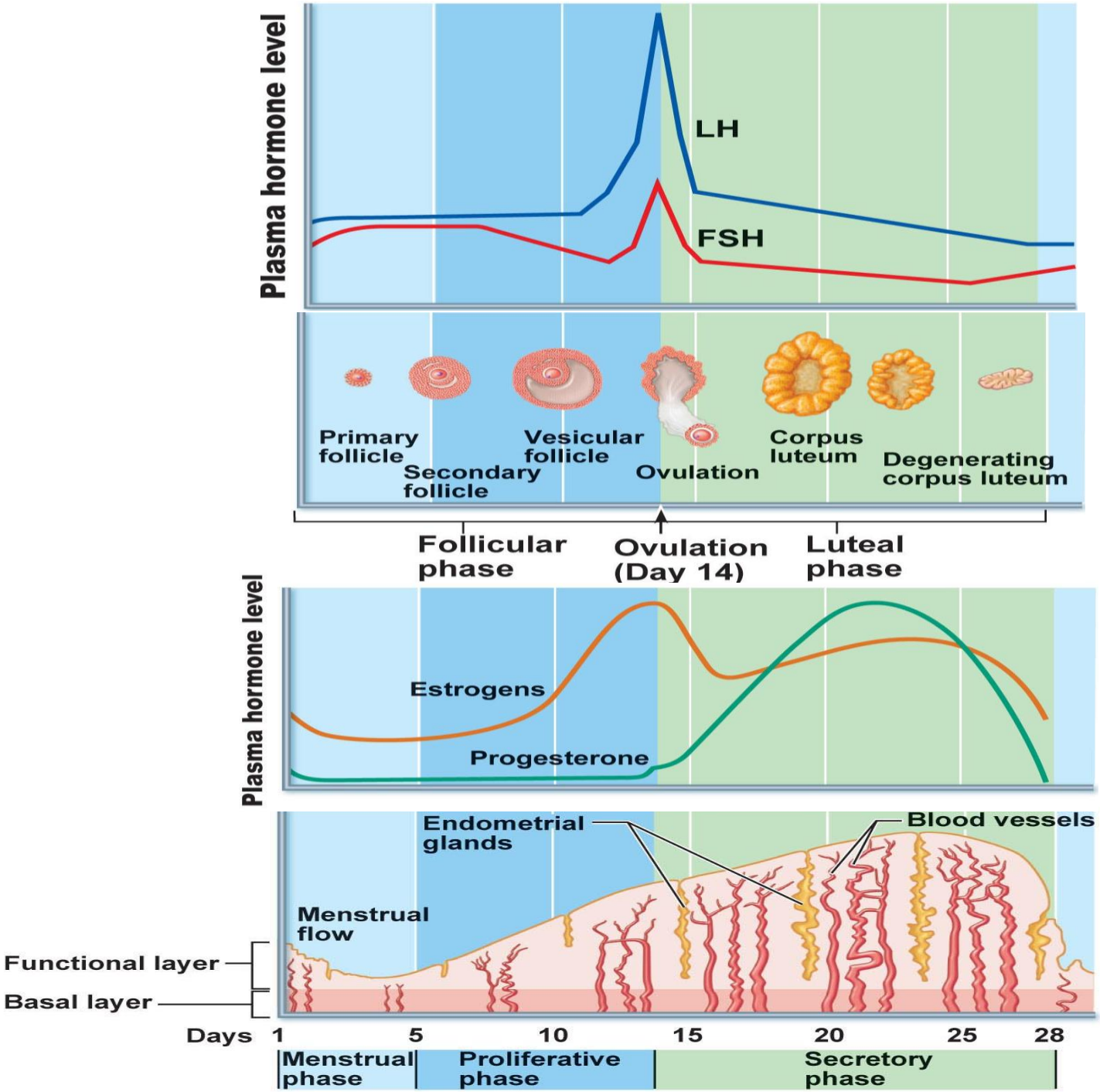


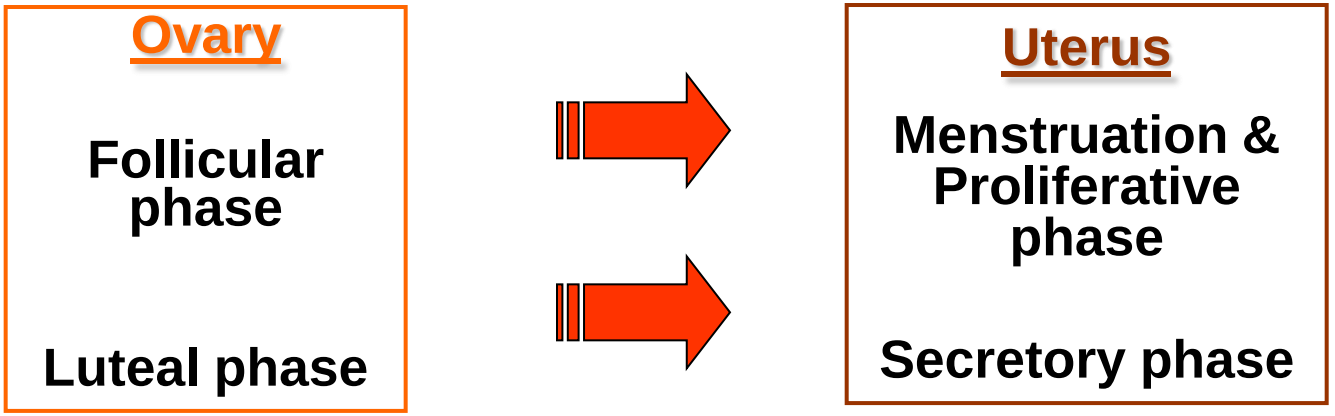
corpus luteum = luteinized granulosa + theca cells + capillaries

unless a pregnancy intervenes, lifespan of CL is <14 days – what is required to maintain CL??

Fig. 27.19


Stimulates
Inhibits
Hypothalamus
GnRH
Travels via portal blood
1
Anterior pituitary
1
FSH
LH
2
2
3 Slightly elevated estrogen and rising inhibin levels.
Thecal cells
Granulosa cells
Androgens
Inhibin
Convert androgens to estrogens
2
Early and midfollicular phases
Hypothalamus
5
4 Positive feedback exerted by large ↑ in estrogen output.
8
5
LH surge
↑Progesterone
↑Estrogens
↑Inhibin
Ruptured follicle
6
8
7
Mature follicle
Ovulated secondary oocyte
Corpus luteum
Late follicular and luteal phases


Plasma hormone level
LH
FSH
Primary follicle
Secondary follicle
Vesicular follicle
Ovulation
Corpus luteum
Degenerating corpus luteum
Follicular phase
Ovulation (Day 14)
Luteal phase
Plasma hormone level
Estrogens
Progesterone
Endometrial glands
Blood vessels
Menstrual flow
Functional layer
Basal layer
Days 1 5 10 15 20 25 28
Menstrual phase
Proliferative phase
Secretory phase



5.4.6 describe the cyclical regulation of the uterine endometrium

Proliferative Phase:

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resurfacing of epithelium

cell **proliferation** in response to ovarian **E**

development of **spiral arteries** & **uterine glands**

Secretory Phase:

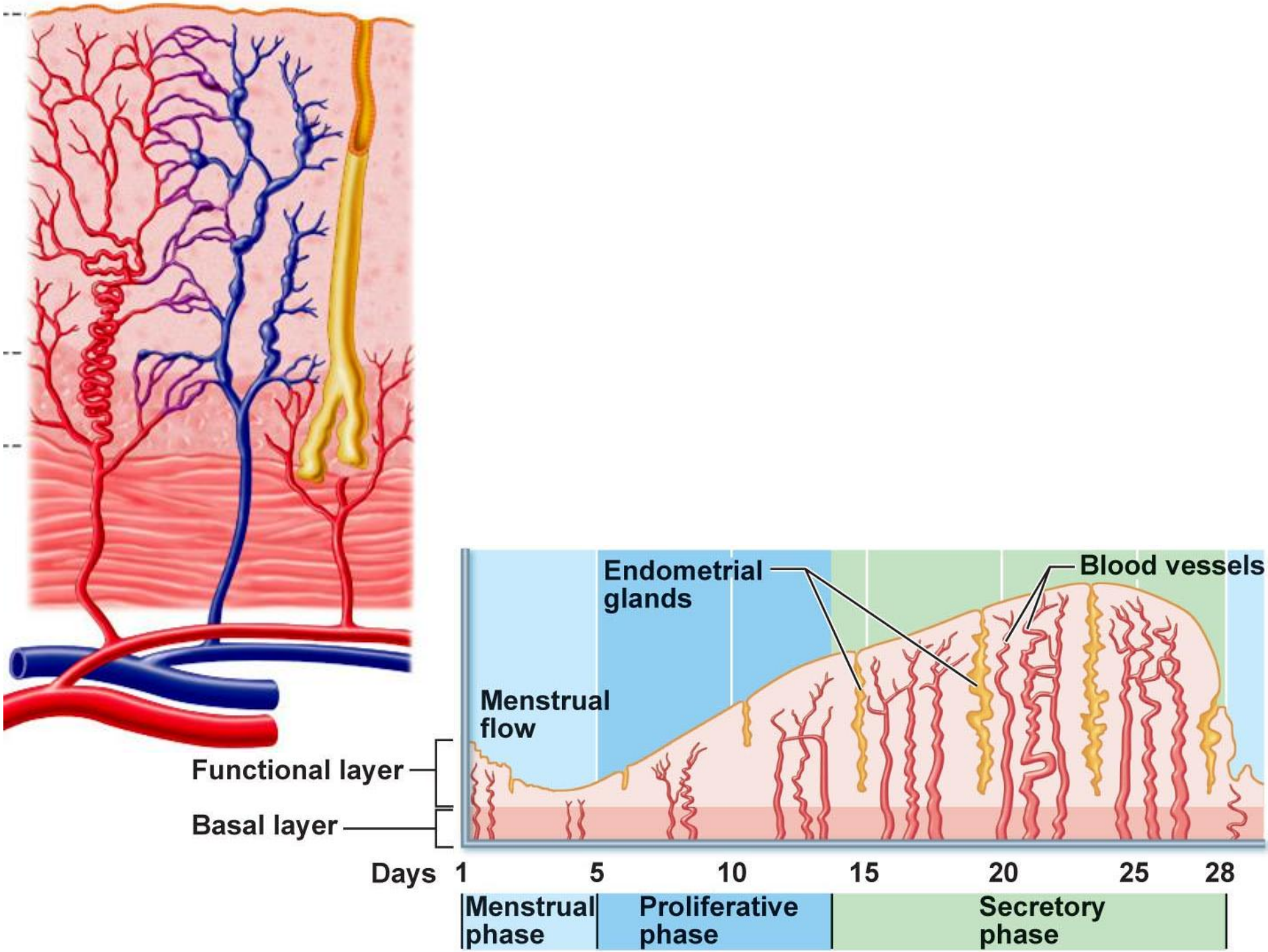
thickening of whole layer due to cell **growth** & **fluid retention**

When is endometrium maximally receptive to embryo implantation?

Why is this called the secretory phase?

as LH levels decline, CL begins to degenerate (~D24) ➢ in absence of P secretion, uterine endometrium is shed & cycle begins again

If oocyte is fertilized: *hCG is produced in increasing amounts beginning D9-13 after ovulation; hCG* ***rescues*** *CL until placental P can maintain pregnancy*


Endometrial glands
Blood vessels
Menstrual flow
Functional layer
Basal layer
Days 1 5 10 15 20 25 28
Menstrual phase
Proliferative phase
Secretory phase

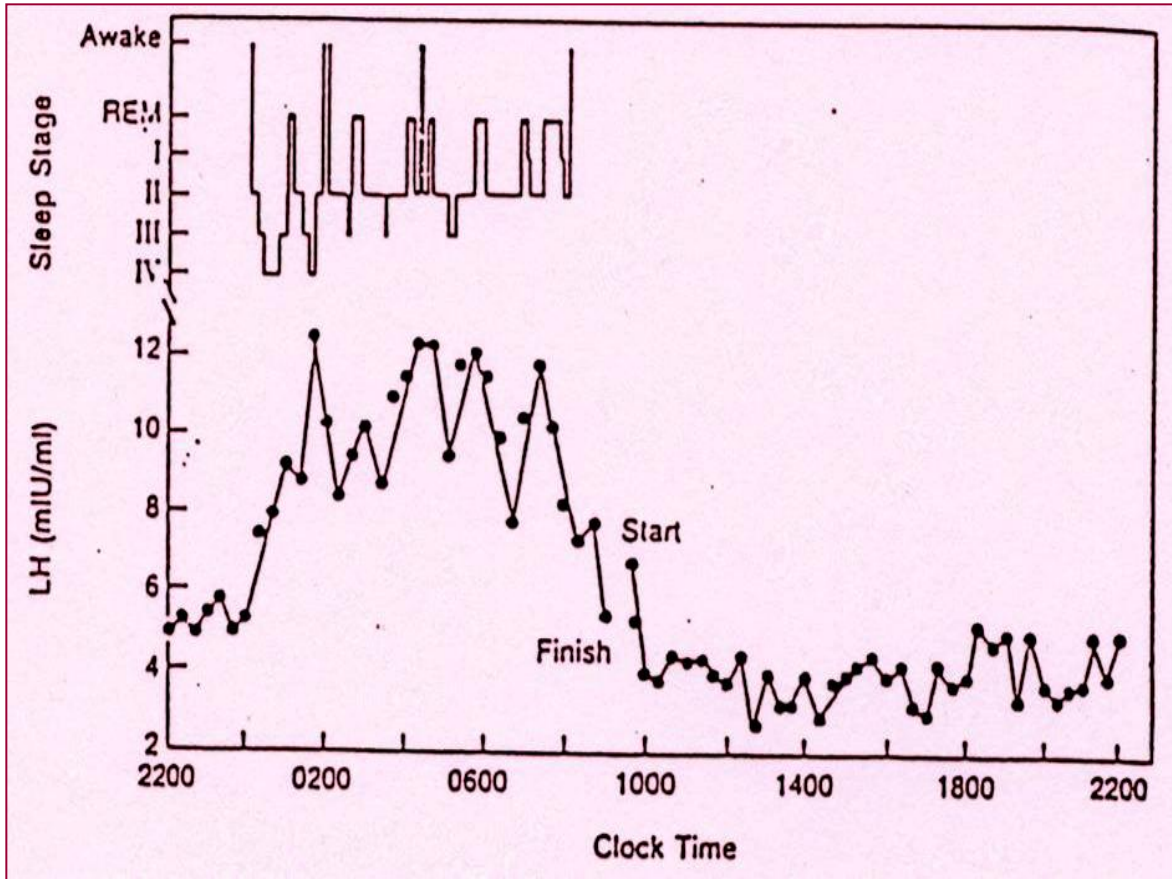
5.4.7 Outline briefly the hormonal regulation of puberty

- initial hormonal events are the same in males & females
- FSH stimulates E secretion by ……..…….. cells (LH stimulation provides T precursor from ……. cells)

estradiol responsible for:

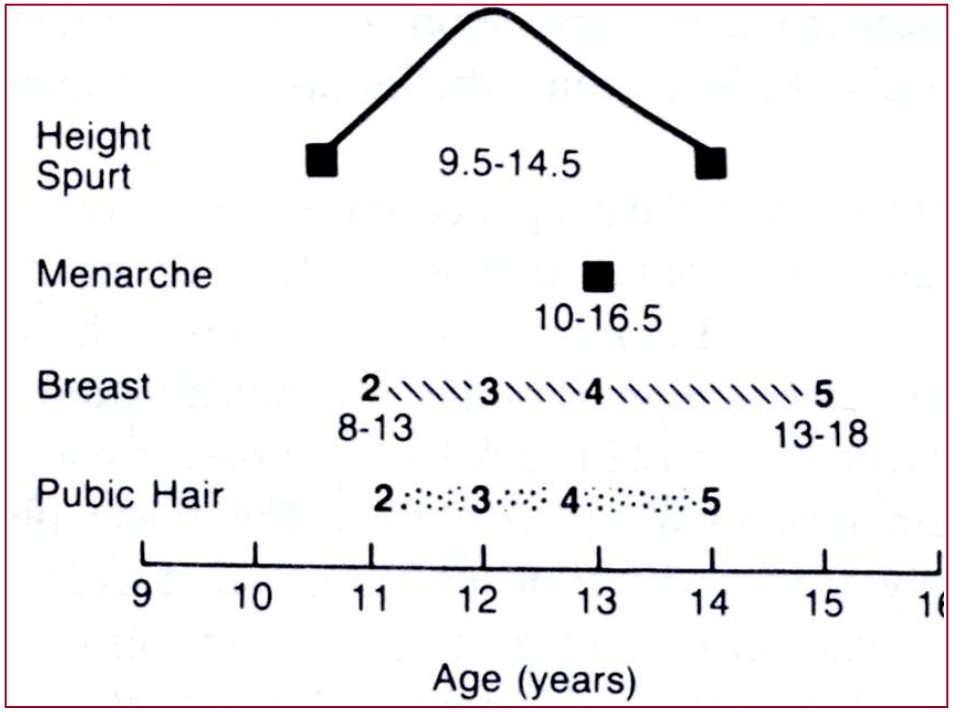
- √ growth & maturation of breasts, reprod. organs
- √ fat redistribution
- √ bone maturation (growth ➢➢➢ closure of epiphyseal plates)

(all processes gradually completed over a ~4-year period)



Puberty (cont):

- cycles of proliferation & regression until sufficient growth occurs that withdrawal of steroid support (atresia of what??) results in first menstruation = **menarche**
- first ovulatory cycle often may not occur until several months later
- concept of a **critical weight** to reach before menarche:
- specifically, a critical **ratio of fat to lean** – ***Why?***



5.4.8 define menopause & summarize its effects on female physiology

DEFINITION: **cessation of menses for at least 12 months**

- **in North America, occurs at mean age of 51.4 years**
- **primary cause is depletion of ovarian follicles**

A. Perimenopause:

- extends from early 40s onward - « transitional years »
- ovarian function begins to wane - deprivation of estrogen (and its effects on FSH/LH secretion) can result in: *hot flushes, insomnia, irritability, fatigue, headaches, depression/mood changes, loss of libido, poor mental performance/ nervousness, loss of skin elasticity*

Menopause

- median age of 51.4 years; can live 1/3 of life after ovaries have ceased functioning

*loss of ovarian E affects all tissues that have **E receptors***

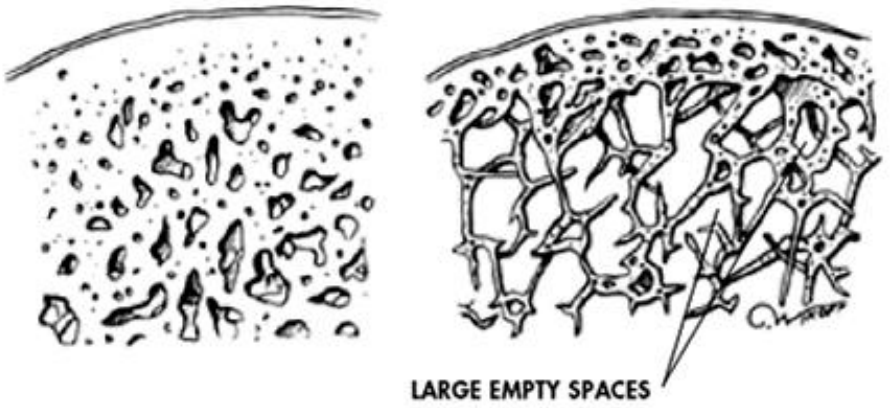
(i) **genital tissues:** atrophy, vaginal dryness, high incidence of vaginal infections)

(ii) **urinary tract:** linings of bladder & urethra have E receptors ➢ urinary frequency, urgency, even incontinence

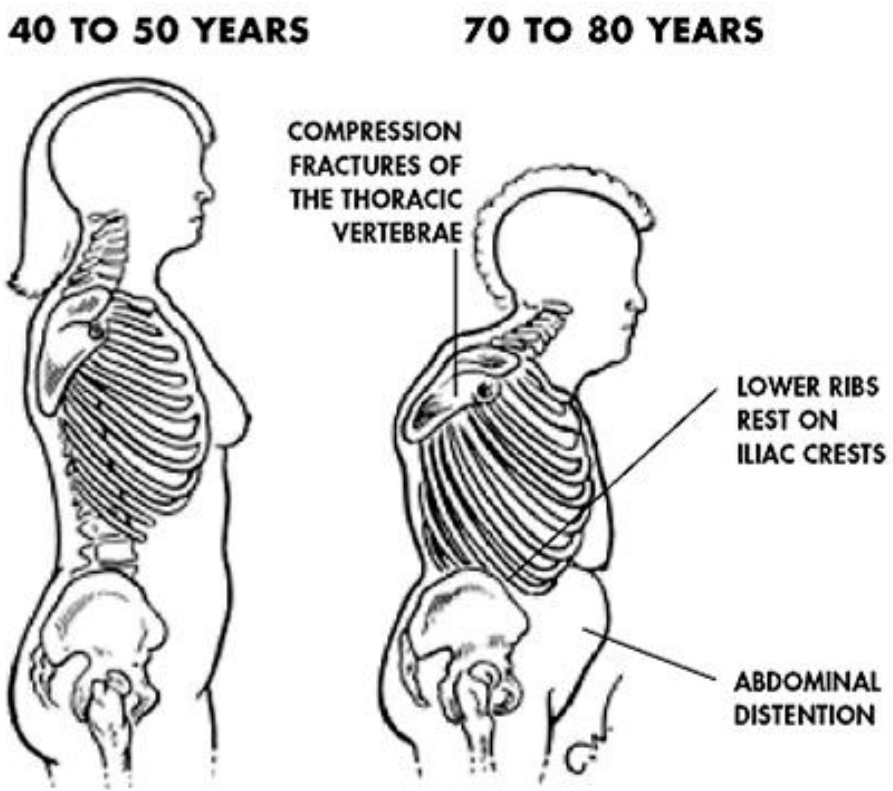
(iii) **breasts:** some atrophy

(iv) **CV system:** atherosclerosis, stroke

(v) **skeleton:** osteoporosis



http://www.healthsquare.com/fgwh/wh1ch30.htm



5.5 Describe the process of oocyte fertilization & summarize the main features of early embryonic development up to implantation

For how long after ovulation is an egg capable of being fertilized?

How long do sperm remain viable in the ♀ reproductive tract?

5.5.1 define sperm capacitation & indicate its relevance to fertility

- a further maturation sperm must undergo to be capable of fertilizing an egg
- occurs following ejaculation once sperm in ♀ tract
- seminal fluid contains capacitation inhibiting factors
- **after capacitation, sperm:**
  - (I) have increased rate of flagellar beat & accelerated motility pattern ➢ ?
  - (ii) plasma membranes are more fragile → facilitates acrosome reaction

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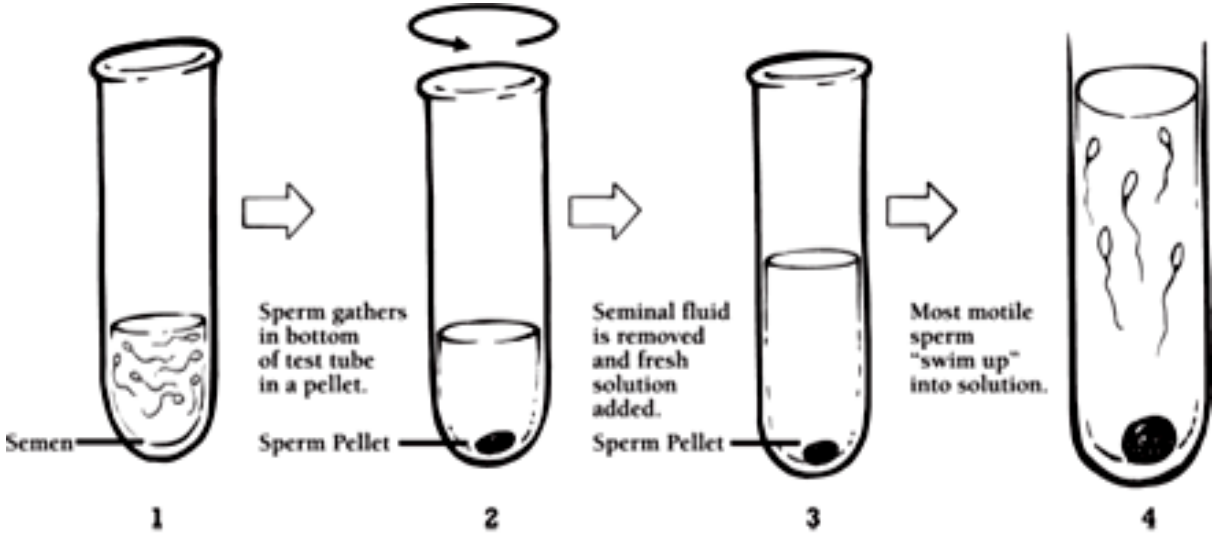
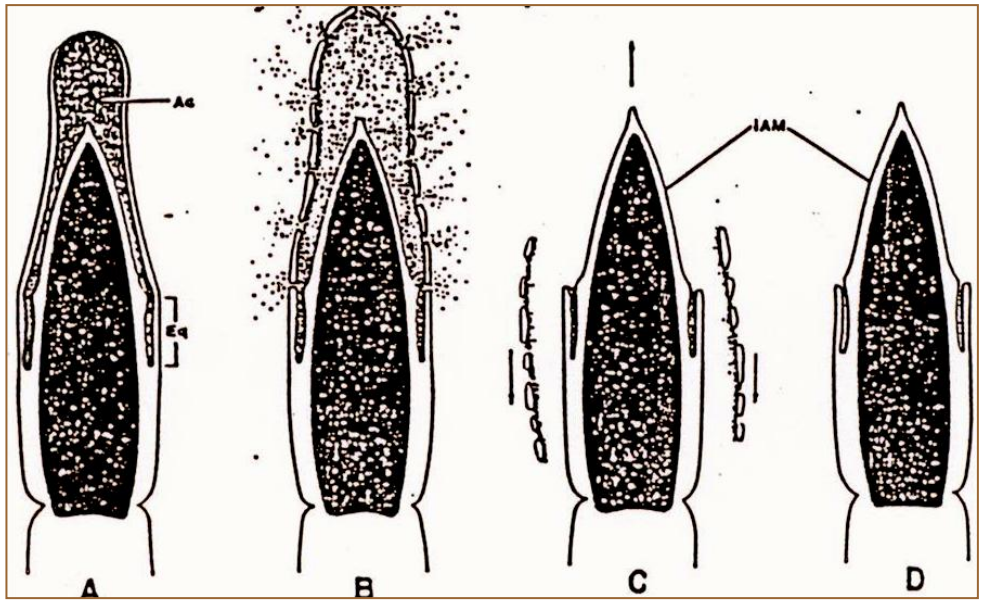
IVF: can induce capacitation by washing sperm or running them through a Percoll gradient → *what is this process accomplishing?*

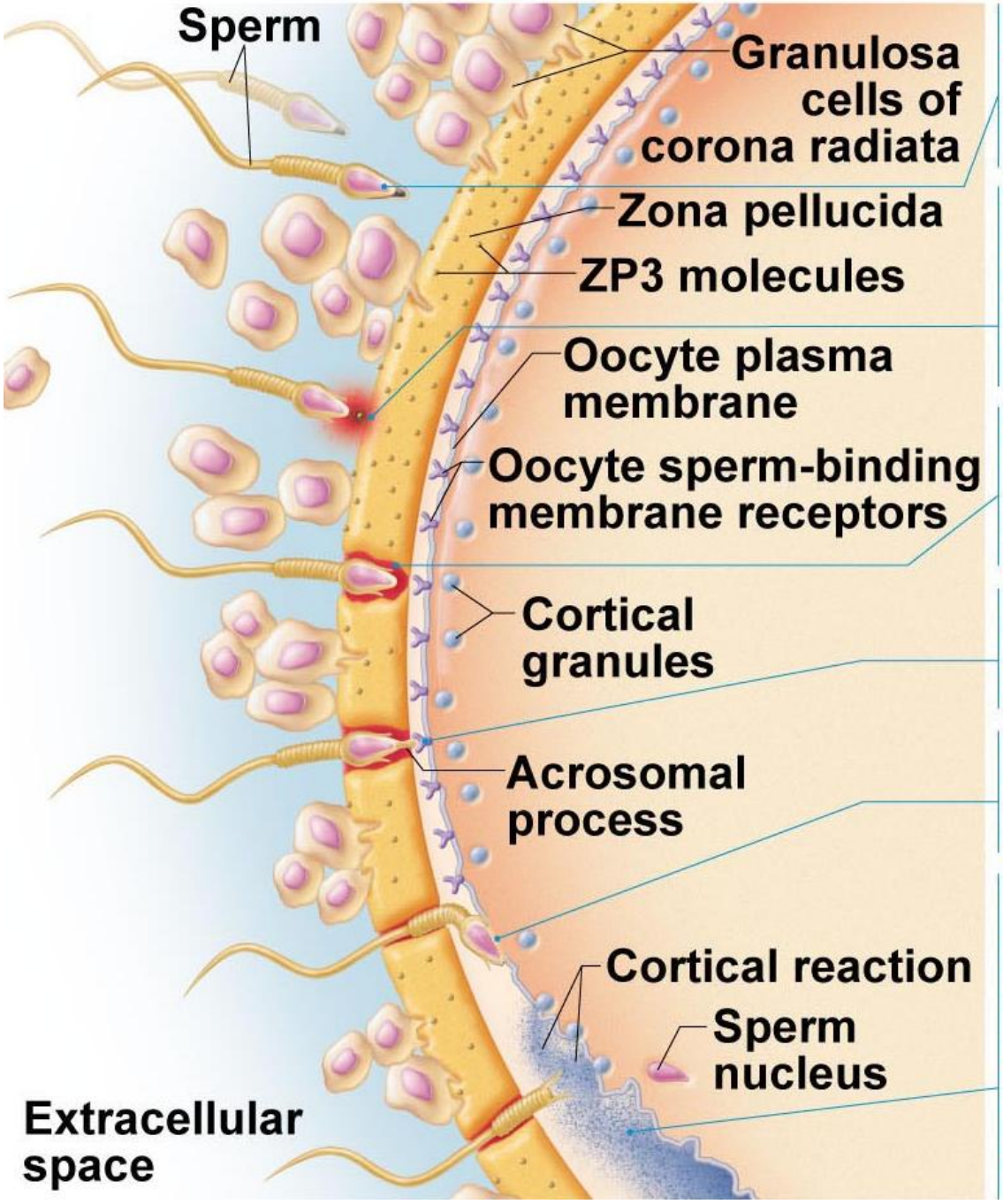


5.5.2 describe the acrosome reaction

- zona pellucida can bind many sperm but only 1 sperm fertilizes the egg
- of ~300 M sperm in ejaculate, only few hundred get close to oocyte (*where is it?*)
- binding of sperm to zp induces acrosome reaction: *What happens and why is this important?*

Why is it important that this happens only after sperm has bound to zp???





1. Aided by surface hyaluronidase enzymes, a sperm cell weaves its way past granulosa cells of the corona radiata.
2. Binding of the sperm to ZP3 molecules in the zona pellucida causes a rise in Ca^{2+} level within the sperm, triggering the acrosomal reaction.
3. Acrosomal enzymes digest holes through the zona pellucida, clearing a path to the oocyte membrane.
4. The sperm forms an acrosomal process, which binds to the oocyte's sperm-binding receptors.
5. The sperm and oocyte plasma membranes fuse, allowing sperm contents to enter the oocyte.
6. Entry of sperm contents causes a rise in the Ca^{2+} level in the oocyte's cytoplasm, triggering the cortical reaction (exocytosis of cortical granules). The result is hardening of the zona pellucida and clipping off of sperm receptors (slow block to polyspermy).

5.5.3 define polyspermy & briefly describe the fast & slow blocks to polyspermy

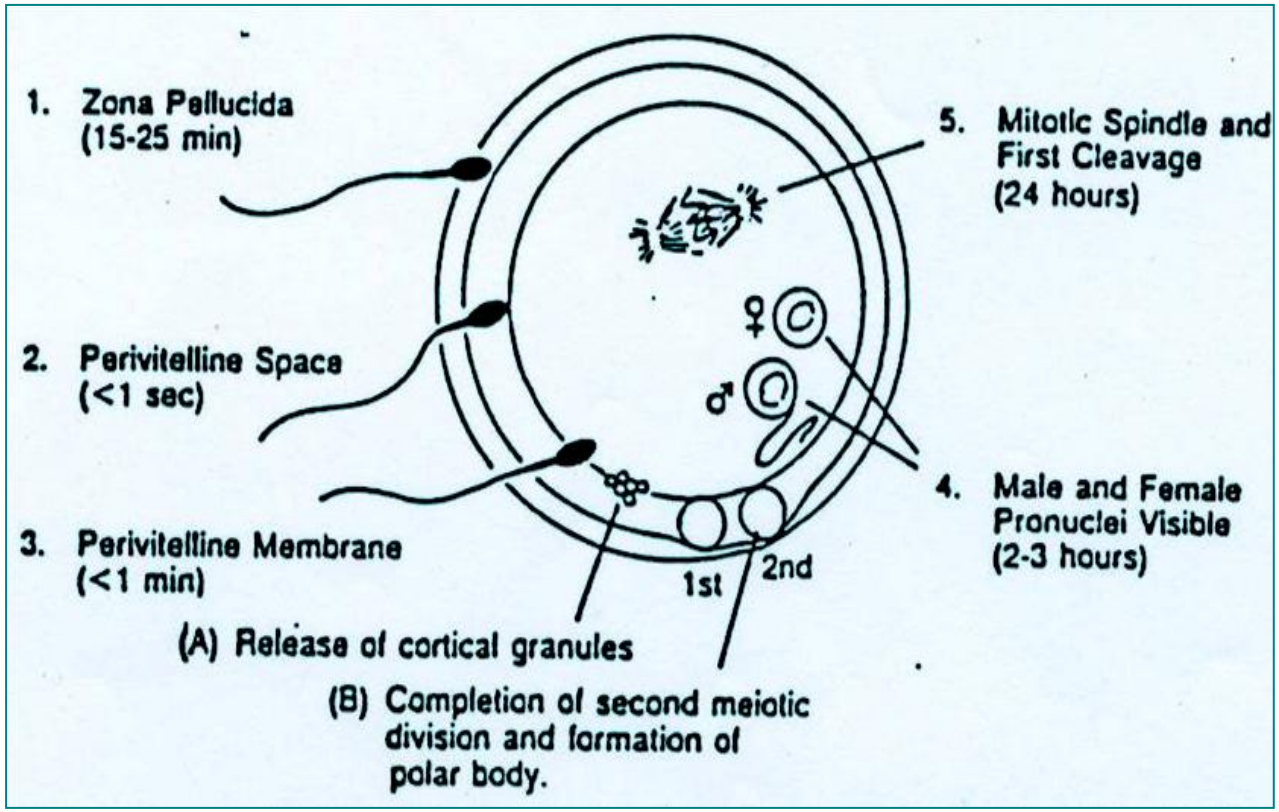
as soon as first sperm penetrates perivitelline membrane:

(i) fast block to polyspermy:

(ii) slow block to polyspermy:

(i) resumption of meiosis, extrusion of 2nd PB, formation of ♀ **pronucleus**

(ii) sperm nuclear material forms ♂ **pronucleus**; ♂ and ♀ pronuclei fuse to form **2N** nucleus of **zygote**



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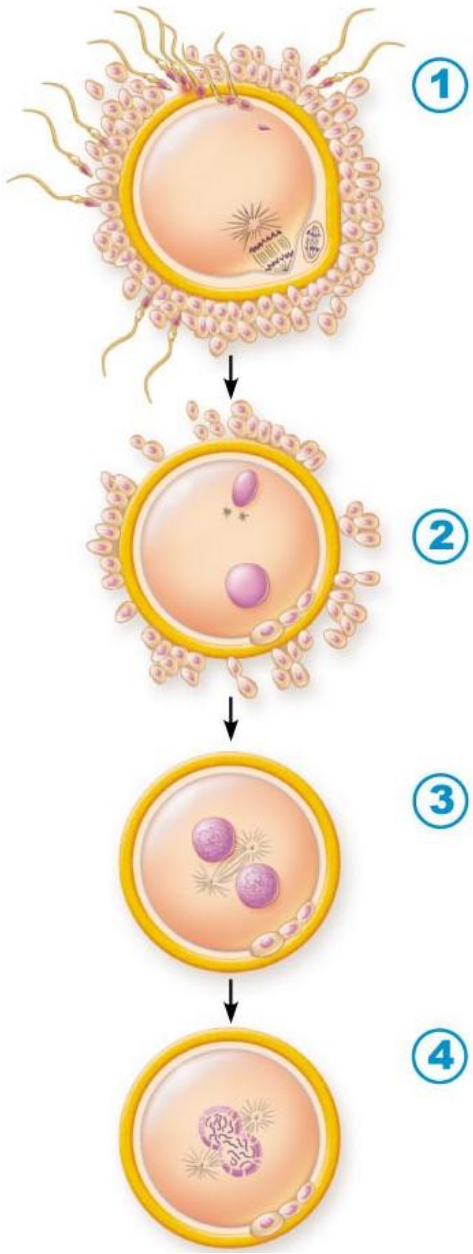


Fig. 29.3

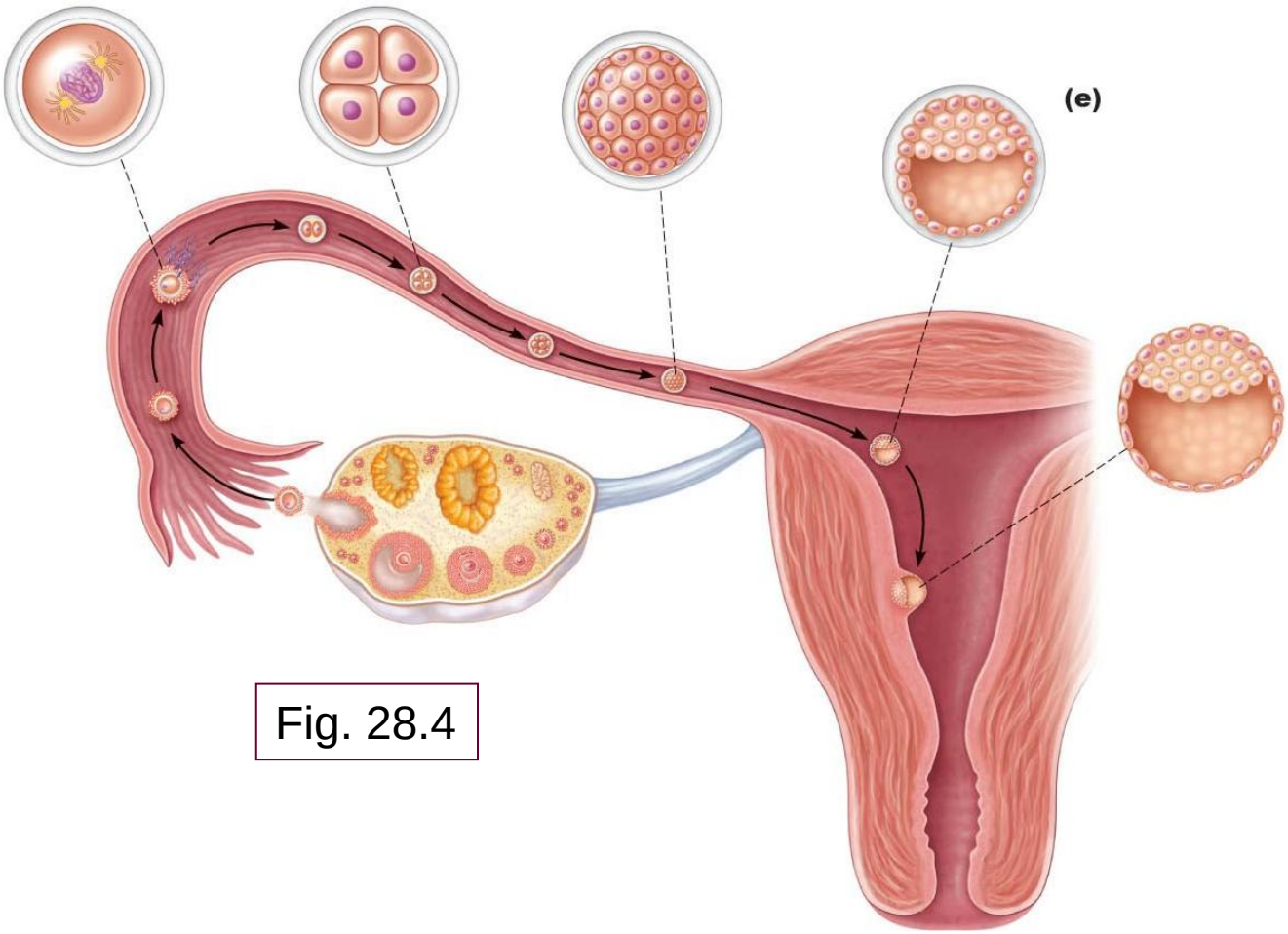


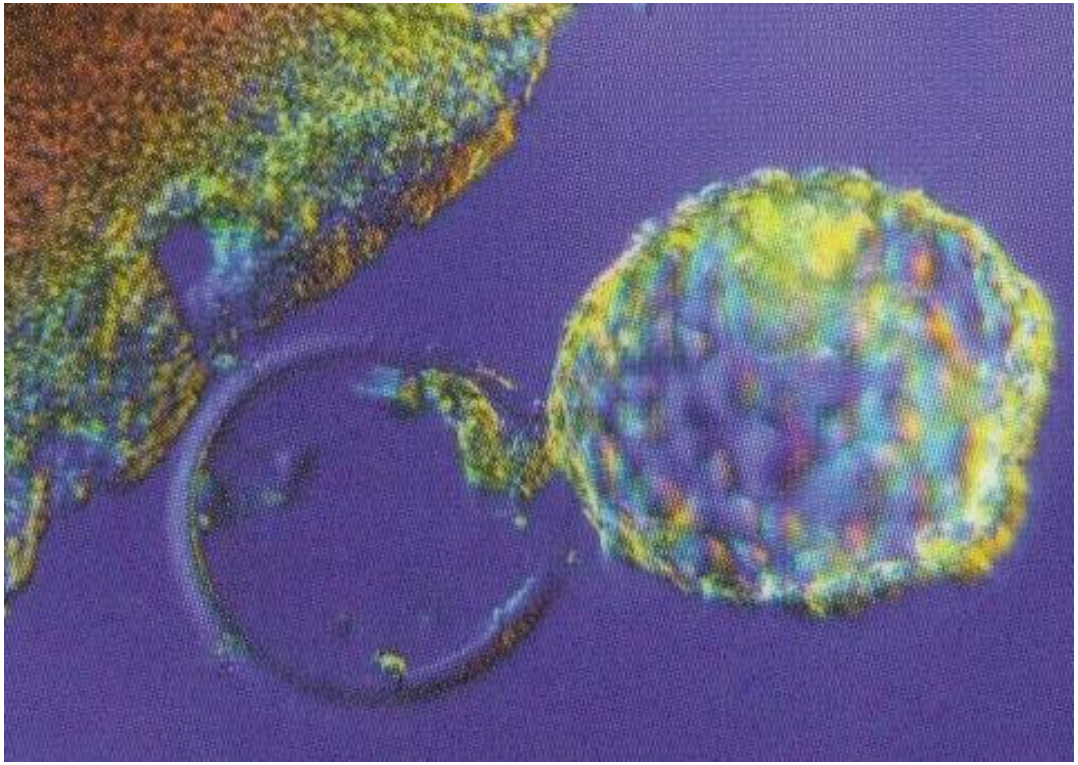
Fig. 28.4

5.5.4 define zygote; summarize the developmental steps that occur while the embryo is traversing the oviduct

5.5.5 define morula, blastocyst, hatching

- **implantation** begins on ~6th day following fertilization:
  - blastocyst burrows into endometrium
  - **trophoblast** cells grow out toward mat blood vessels

What is happening here?



http://www.gdsb.org.cn/syzs/syzs.htm

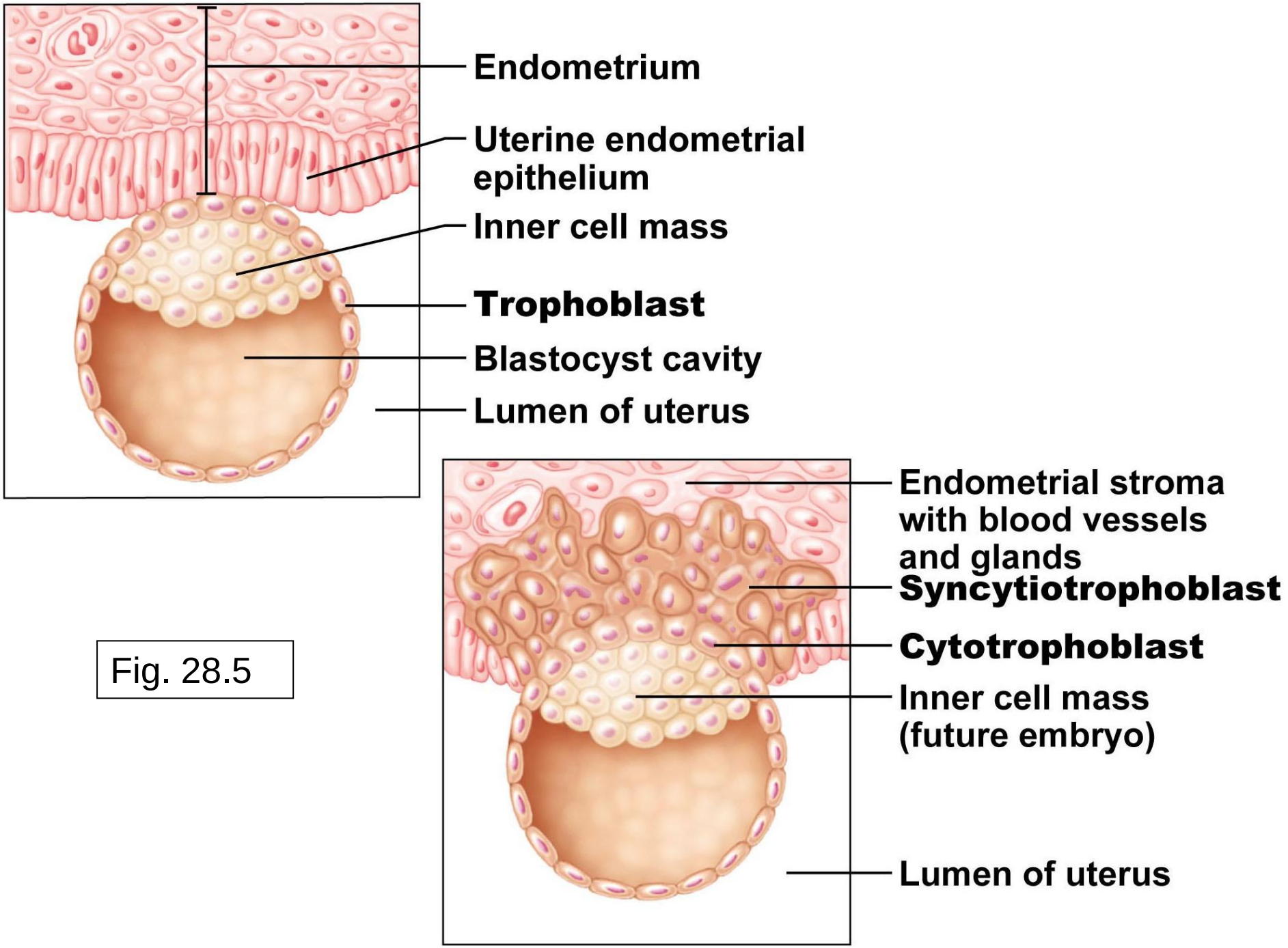

Endometrium
Uterine endometrial epithelium
Inner cell mass
Trophoblast
Blastocyst cavity
Lumen of uterus
Endometrial stroma with blood vessels and glands
Syncytiotrophoblast
Cytotrophoblast
Inner cell mass (future embryo)
Lumen of uterus

Fig. 28.5

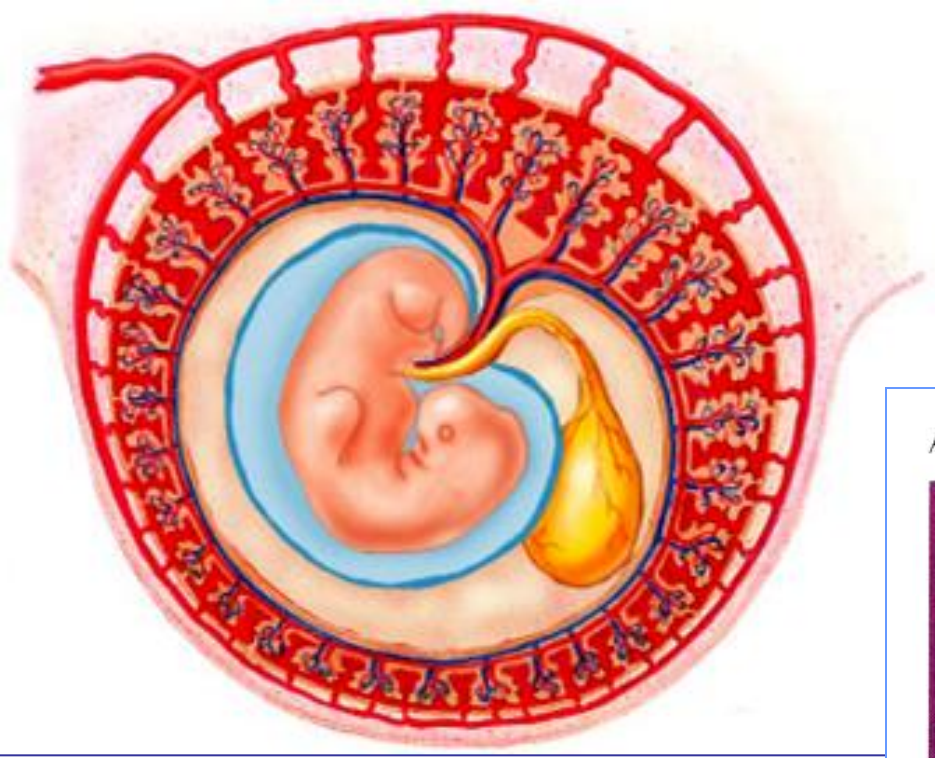
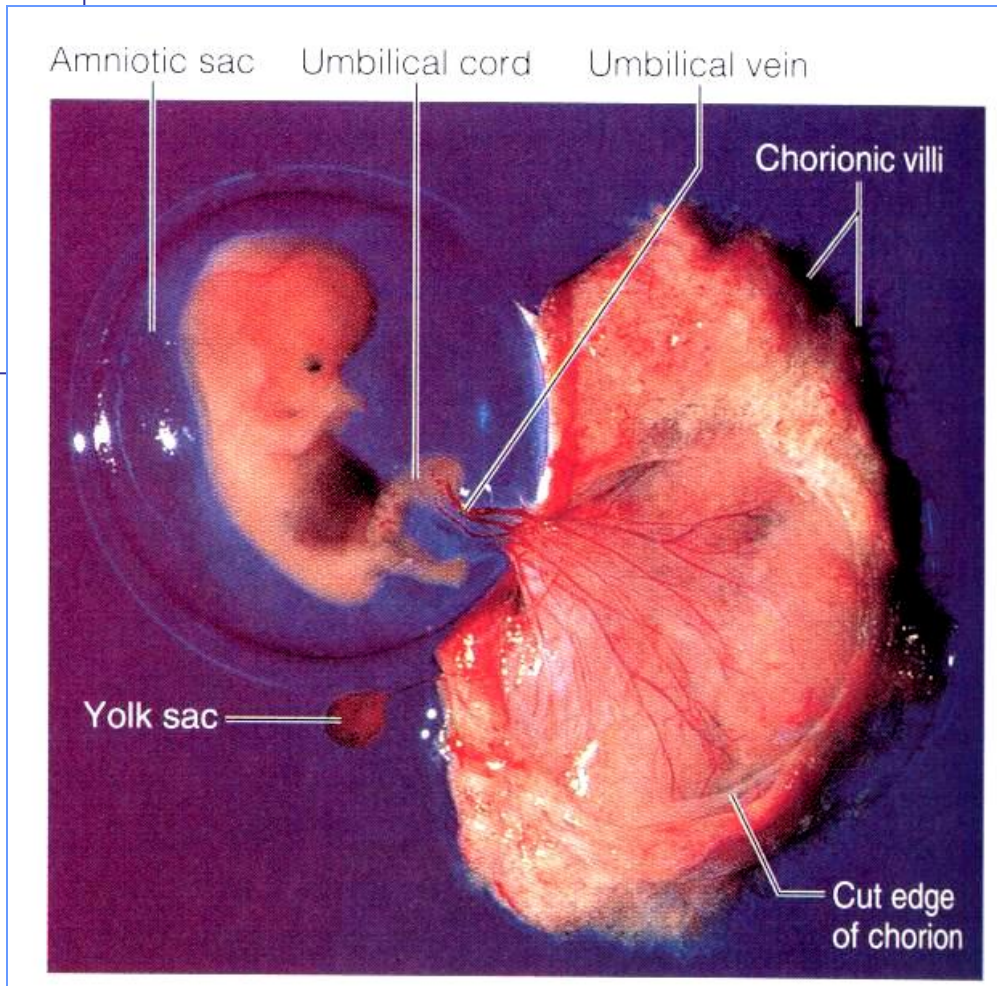


Fig. 28.7



(e) 7-week embryo

Conception to 2 weeks --- Germinal Period

3 to 8 weeks --- Embryonic Period

9 weeks to term --- Fetal Period

5.6 Summarize the hormonal regulation of pregnancy, parturition & lactation

Placentation

maternal and fetal blood supplies NOT in direct contact; nutrients, gases, wastes diffuse through:

(i) trophoblast
(ii) mesenchyme
(iii) fetal capillary endothelium

normal term placenta is ~500g, measures 15-20 cm diam, 2-3 cm thick

umbilical cord usu 50-70 cm in length; contains 2 umbilical arteries, 1 umbilical vein

*What is the **foramen ovale**?*

*What is the **ductus venosus**?*

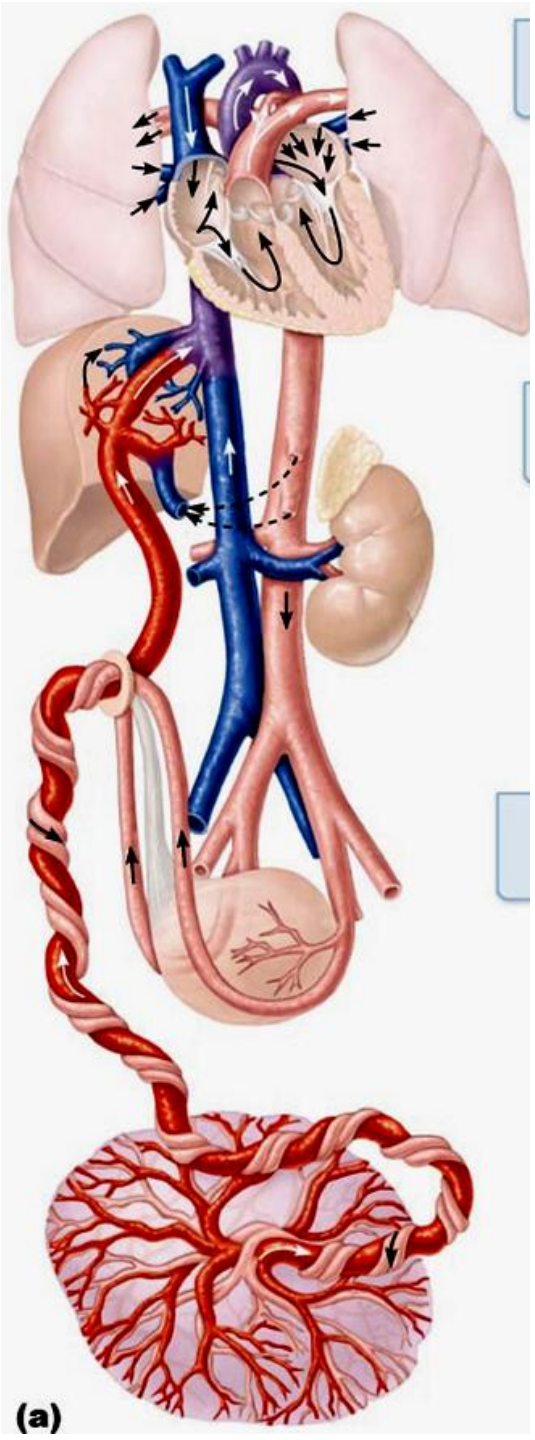


Fig. 28.14

5.6.1 describe the dual functions of the placenta: ***endocrine*** *&* ***exchange***

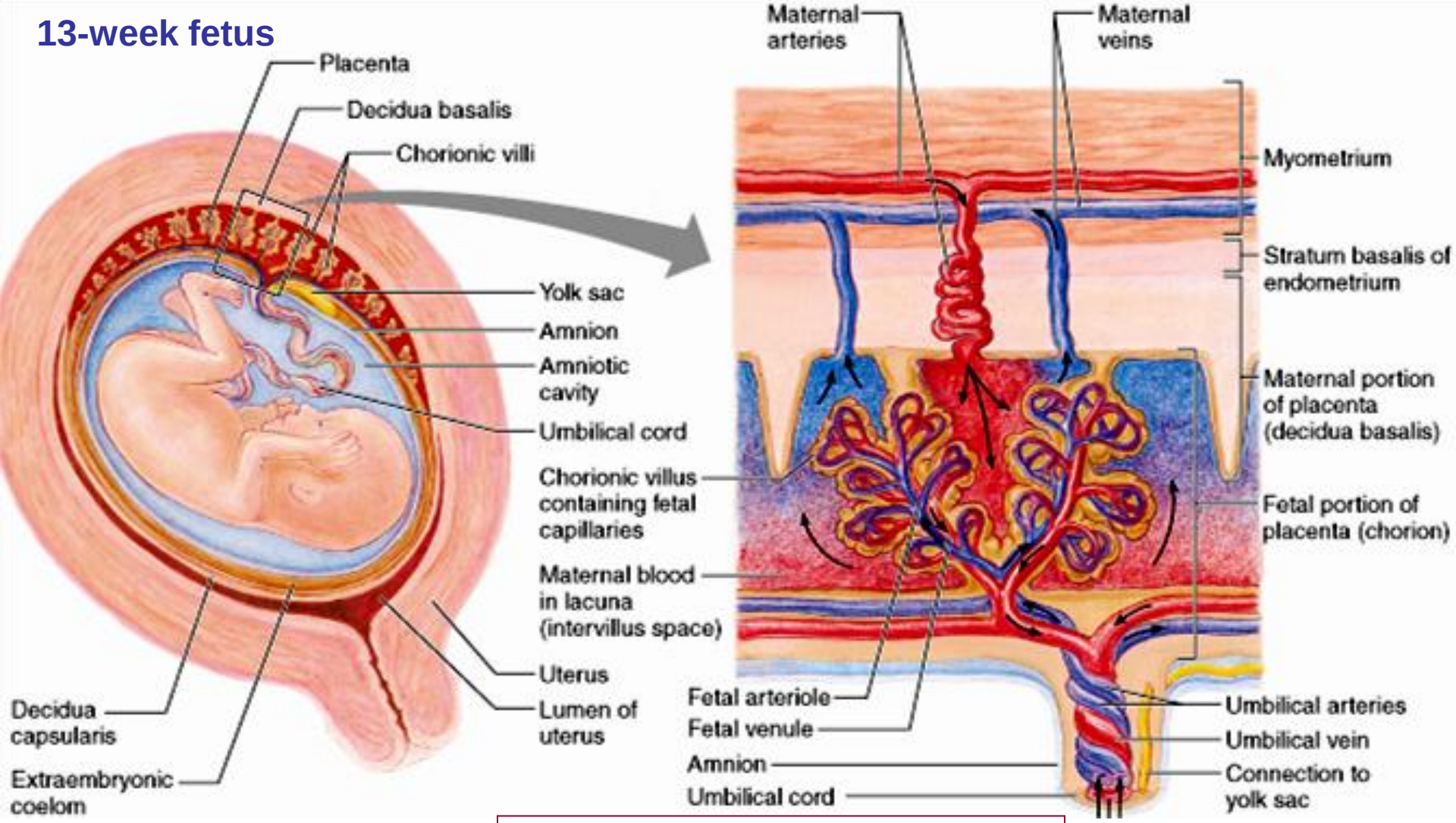


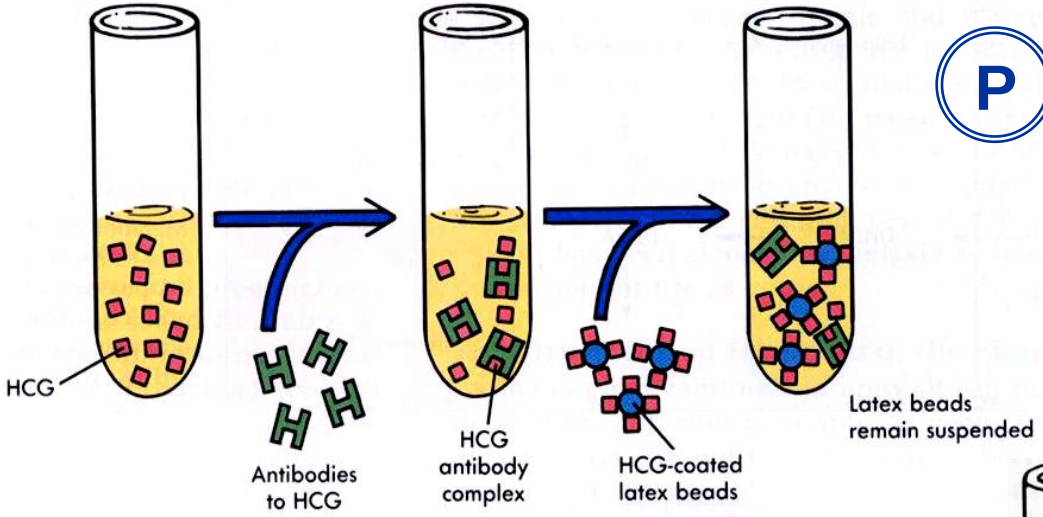
Fig 28.8: Placental exchange

HORMONES:

Human Chorionic Gonadotropin (hCG)

- present in maternal serum by 8th day after fertilization; levels peak by ~60-80 days, then begin to decrease

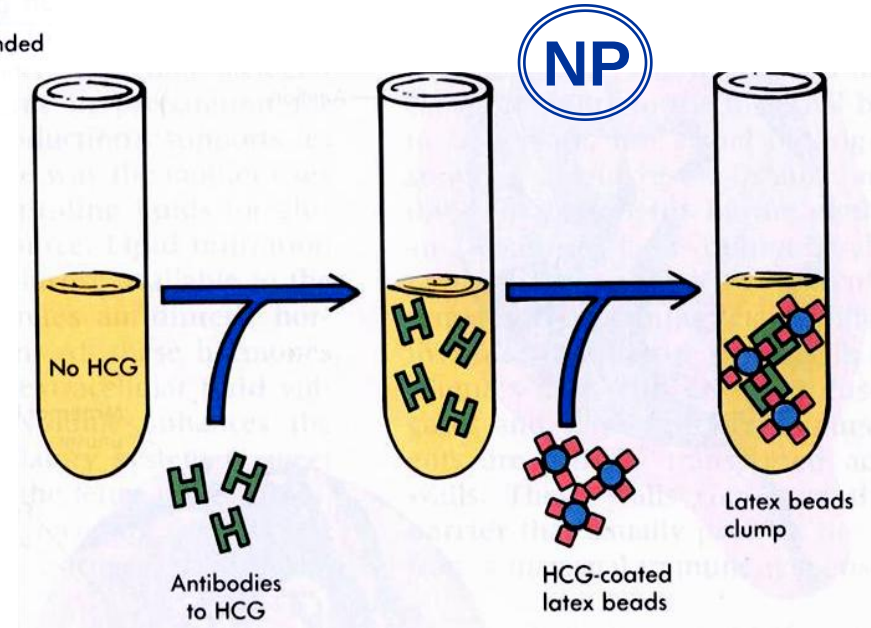
What is the primary function of hCG?? How does this relate to the timing of its production and secretion by the developing embryo/fetus??



P

can detect pregnancy by 3 days after missed period

based on detection of hCG in blood or urine



S,M&M

b) Human placental lactogen (hPL)

- structurally similar to GH & prolactin (also = human chorionic somatomammotropin)
- placenta begins to secrete hPL during 1st trimester; levels increase until delivery
  - (i) stimulates breast development in preparation for postnatal lactation
  - (ii) supports fetal bone growth
  - (iii) makes glucose available to fetus = *diabetogenic or anti-insulin effect*

c) Estrogens

- initially come from_____; function gradually assumed by placenta
- placenta converts circulating androgens (fetal & maternal adrenal glands) to estrogen
- initially estrone & estradiol-17-β, then estriol
  - (i) maintains uterine endometrium
  - (ii) contributes to breast development

d) Progesterone

- initially from _____; function gradually assumed by placenta
- levels gradually increase over the course of the pregnancy
- a **relaxing** effect on smooth muscle:
  - (i) uterus: _____
  - (ii) blood vessel walls: _____
  - (iii) ureters: _____
  - (iv) GE sphincter: _____
  - (v) intestines: _____

5.6.2 outline briefly the influences of pregnancy on the CV, digestive, urinary & reproductive systems of the mother

A) Cardiovascular:

bp decreases slowly to nadir @ 24 wks; then slowly back up to NP values

pulse slowly increases to max of 15-20 beats/min above NP in 3rd trimester

myocardial hypertrophy, increased contractility

- overall increase in blood volume (~40%): plasma by ~45% & RBCs by 20-30% ⇒ *what is the **physiological anemia of pregnancy**???*

B) GI tract:

- nausea: increased progesterone, hCG, both???
- when severe: ***hyperemesis gravidarum***; if untreated can lead to dehydration, ketosis, electrolyte derangements, liver and kidney damage

C) Urinary tract

kidneys increase in length by 1-1.5 cm (increased renal blood flow)

bladder tone decreases; bladder capacity nearly doubles

glomerular filtration rate (GFR) increases by 30-50% in first trimester

high progesterone promotes renal Na (& water) loss; but increased aldosterone & estrogen promote salt & water retention

increased risk of urinary tract infections – *why???*

D) Cervix:

softening & increased vascularity from early in 1st trimester

increased production of mucus by endocervical glands

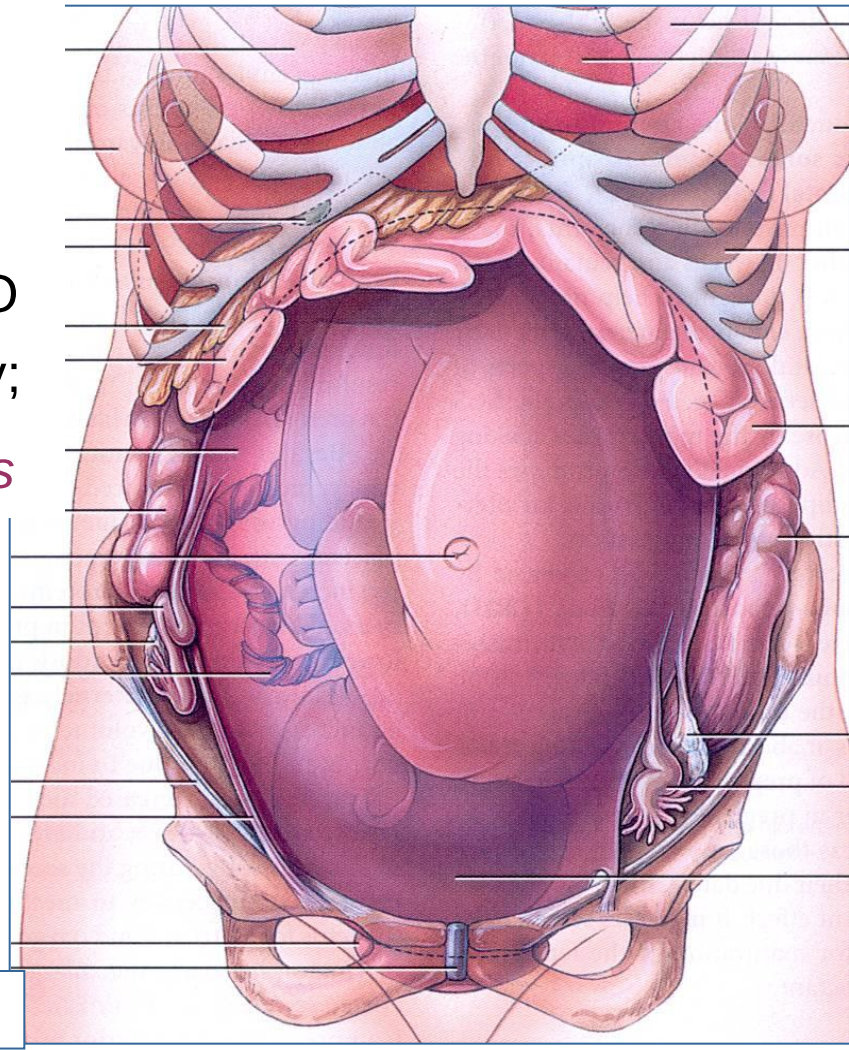
E) Vagina:

cervical secretions increase in quantity; decrease in pH (hi estrogen)

increased susceptibility to vaginal candidiasis (fungal infection; hi estrogen, hi glycogen)

F. Uterus:

- enlarges by hypertrophy from 50-70 g (NP) to ~1000 g at term (effects of _____ & ____)
- during 2nd trimester, uterus moves out of pelvis & begins to displace intestines up
- by 36th week, intestines pushed up to just beneath diaphragm ➢discomforts experienced by mother include ____ ____ & _____
- blood flow to uterus at term ~500-750 ml/min (10x NP level); = 10-20% total CO
- contracts every 5-20 min during pregnancy; irregular contractions that are not coordinated = *Braxton Hicks contractions*



T&G

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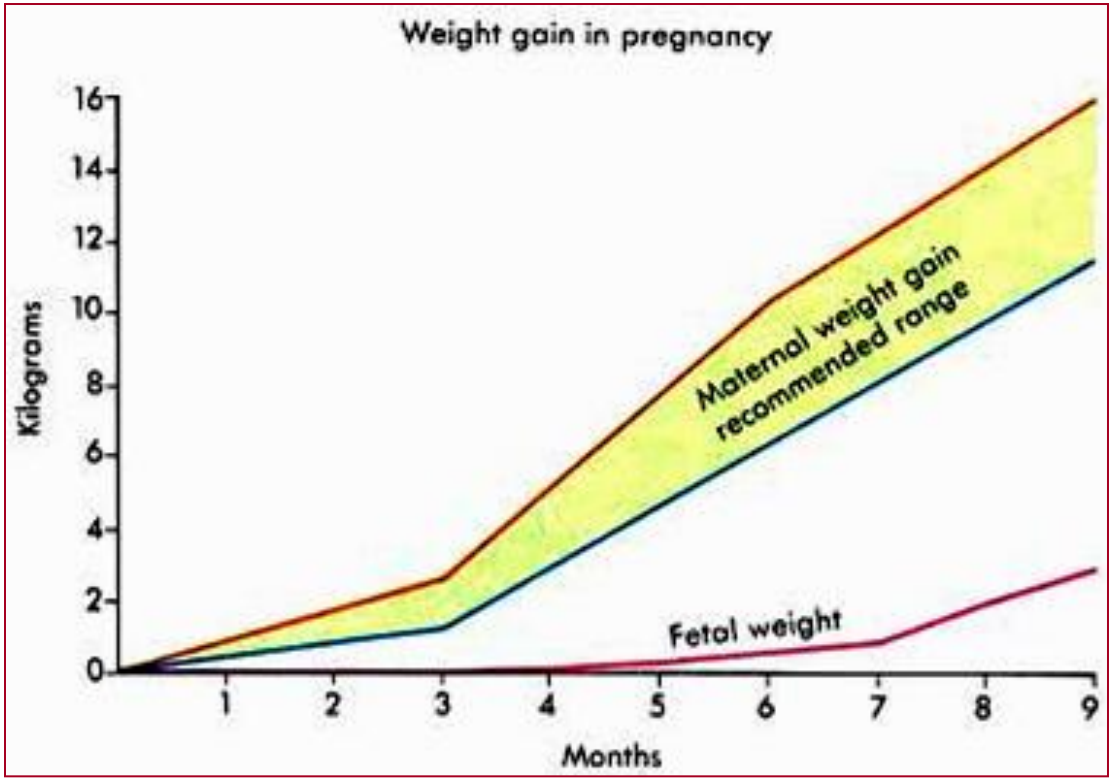
5.6.3 reminder of the importance of good nutrition during pregnancy

- balanced diet (protein, carbohydrates, fats, vitamins, minerals, fiber)
- important vitamins include vitamin D ( ), folic acid ( ), vitamin K ( )
- important minerals include iron ( ), calcium ( )



Component	*Weight (kg)*
Baby	3.2
Placenta	0.5
Amniotic fluid	0.9
Breasts	0.9
Blood	1.4
Uterus	0.9
Other	8.1
TOTAL	15.9

5.6.4 list the 3 stages of parturition

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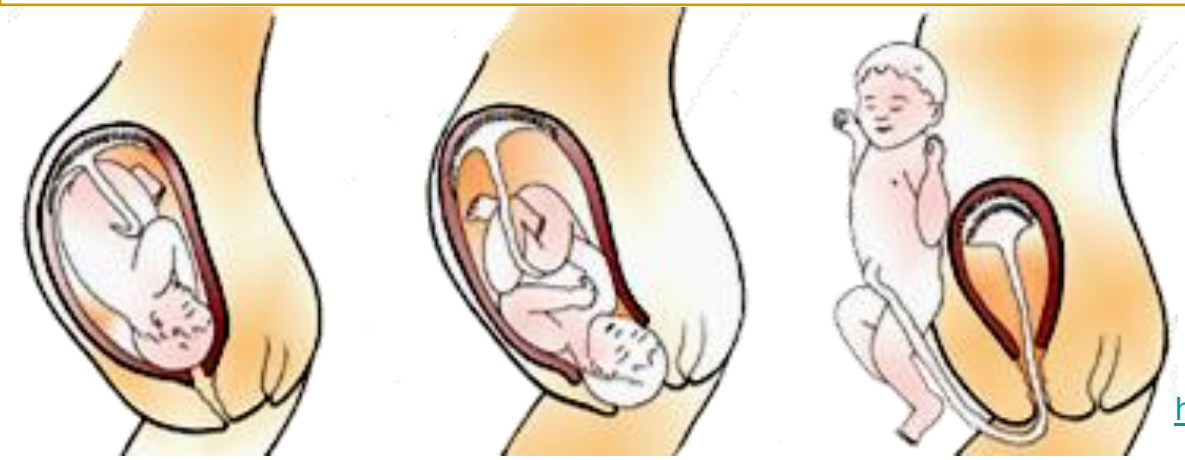
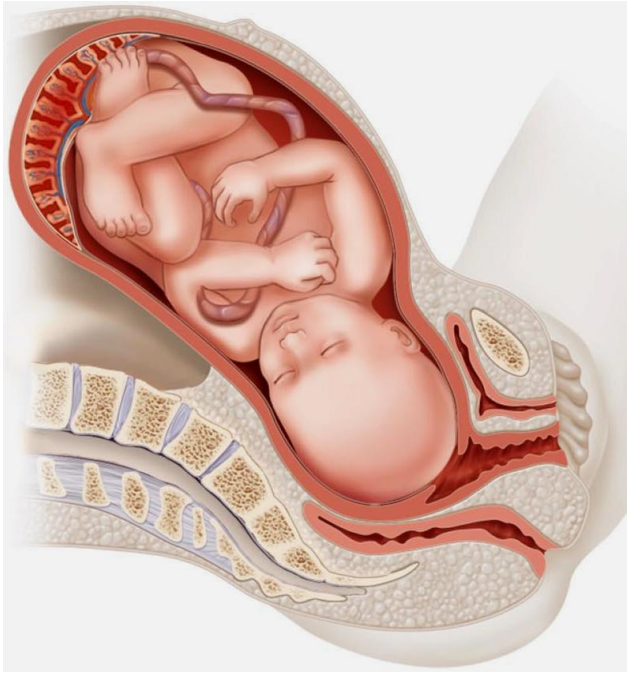
- whole process is not completely understood – esp. what is the signal to initiate parturition and how can we stop premature labour and delivery??
- estrogen levels **highest** toward time of parturition:
  - (1) lots of **oxytocin** receptors on myometrial cells
  - (2) antagonizes relaxing effect of **progesterone**
- two hormones important during labour and delivery:
  - (1) **oxytocin** – source?
  - (2) **prostaglandins** – source?

Stages:

1) **DILATATION:** uterine contractions dilate cervix up to 10 cm; variable in duration
2) **EXPULSION:** complete cervical dilation to birth (minutes to few hours)
3) **PLACENTAL:** delivery of placenta;15 min after birth



http://www.shinesa.org.au/images/Stages-of-birth.gif

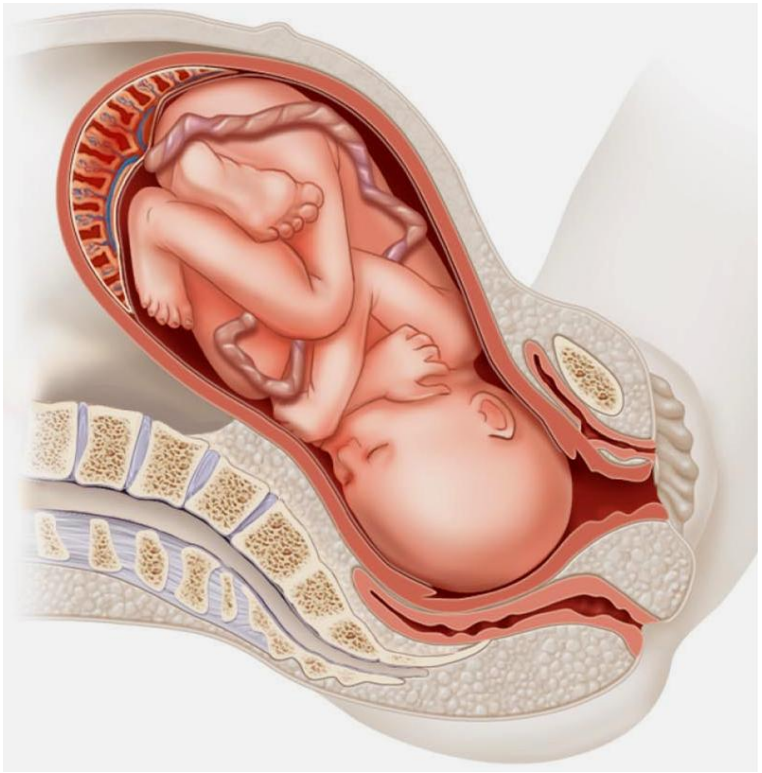


5.6.5 summarize the neuroendocrine regulation of the onset & completion of parturition

(i) Baby moves into birth canal; pressure of head on cervix ⇒ neuroendocrine reflex – result??

(ii) Oxytocin stimulates uterus to synthesize prostaglandins ➢ effects?

Fig. 28.18a,b



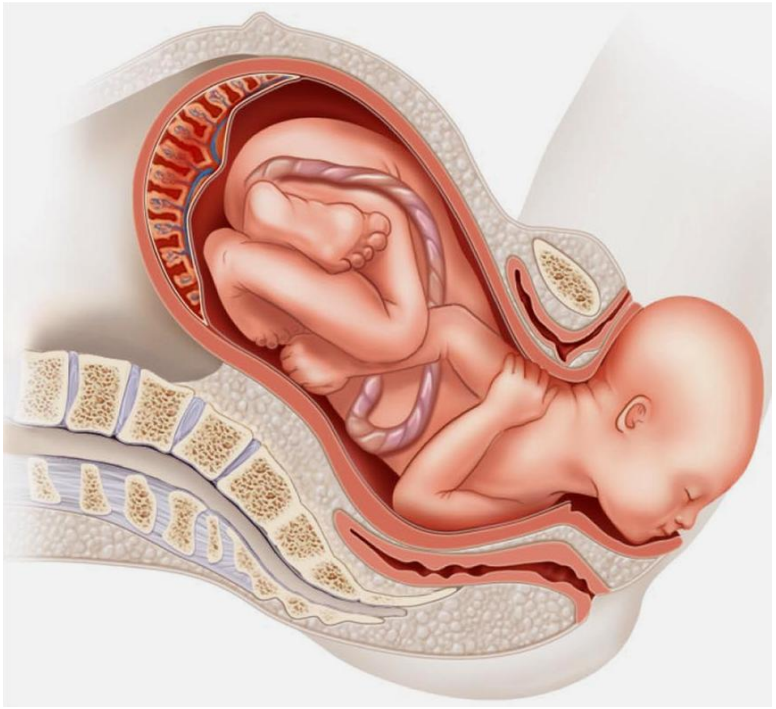
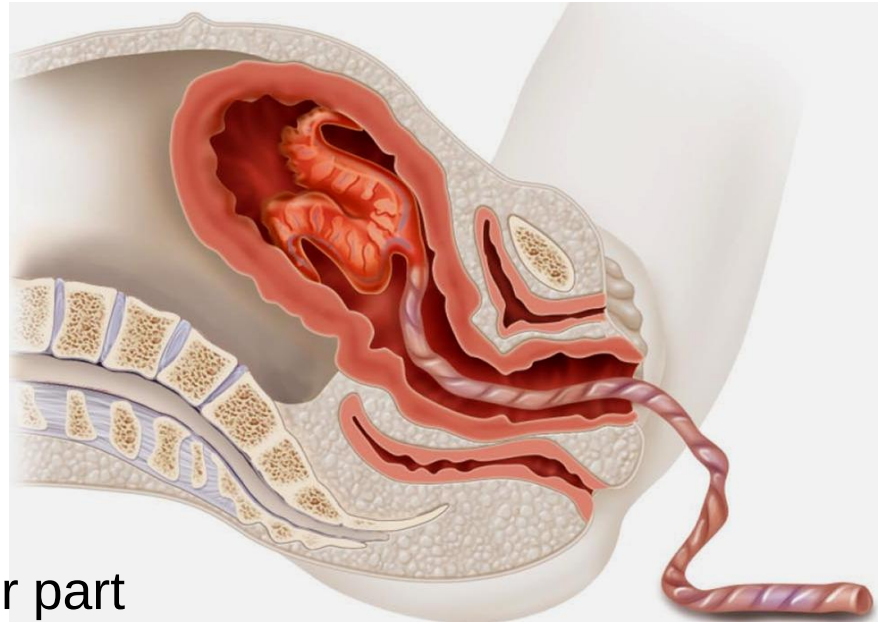


Fig. 28.18c,d



(iii) Oxytocin levels are high during latter part of pregnancy, but labour not initiated because:

- √ progesterone levels also high
- √ insufficient oxytocin receptors

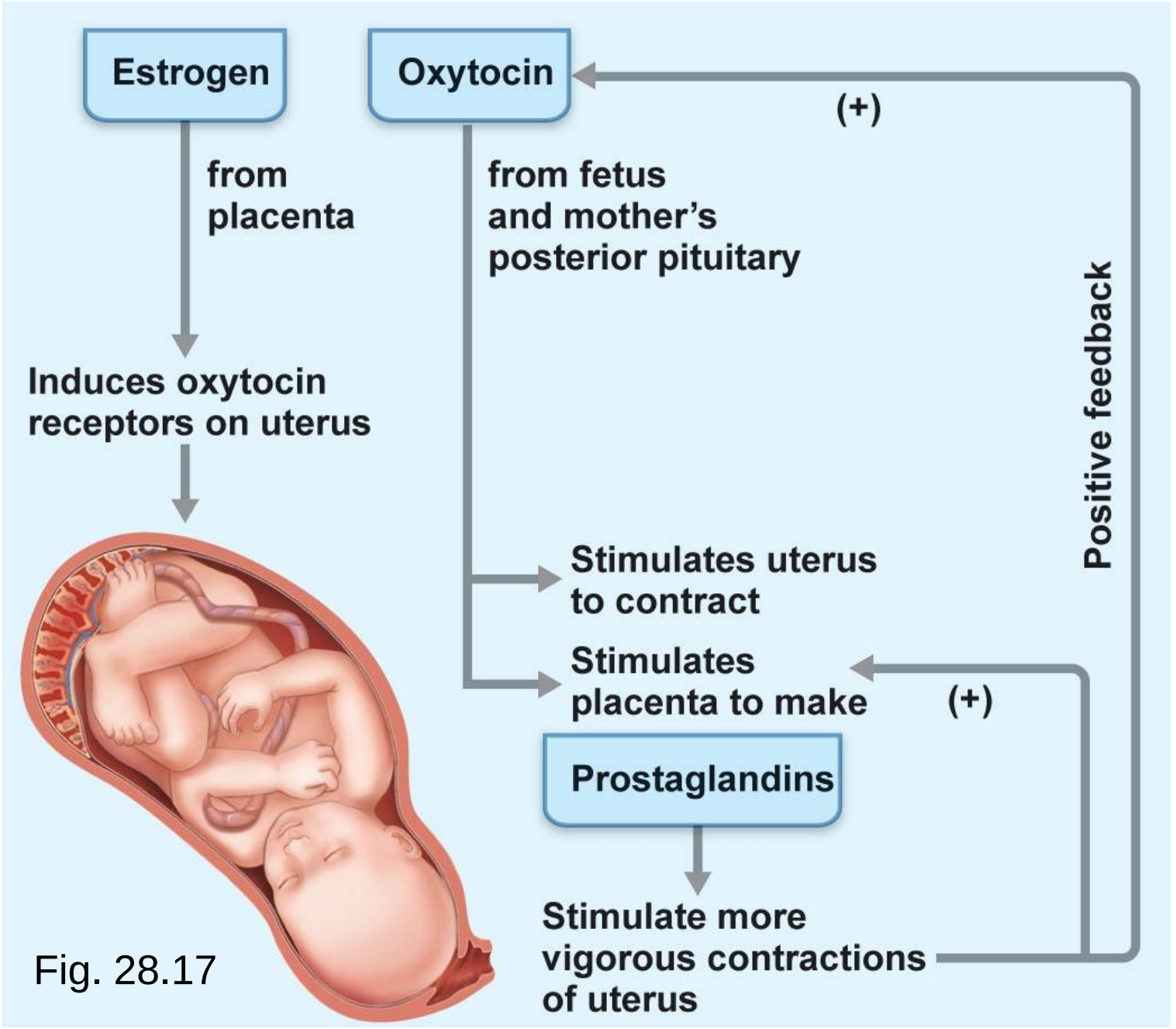

Estrogen
Oxytocin
(+)
from placenta
from fetus and mother's posterior pituitary
Positive feedback
Induces oxytocin receptors on uterus
Stimulates uterus to contract
Stimulates placenta to make
(+)
Prostaglandins
Stimulate more vigorous contractions of uterus

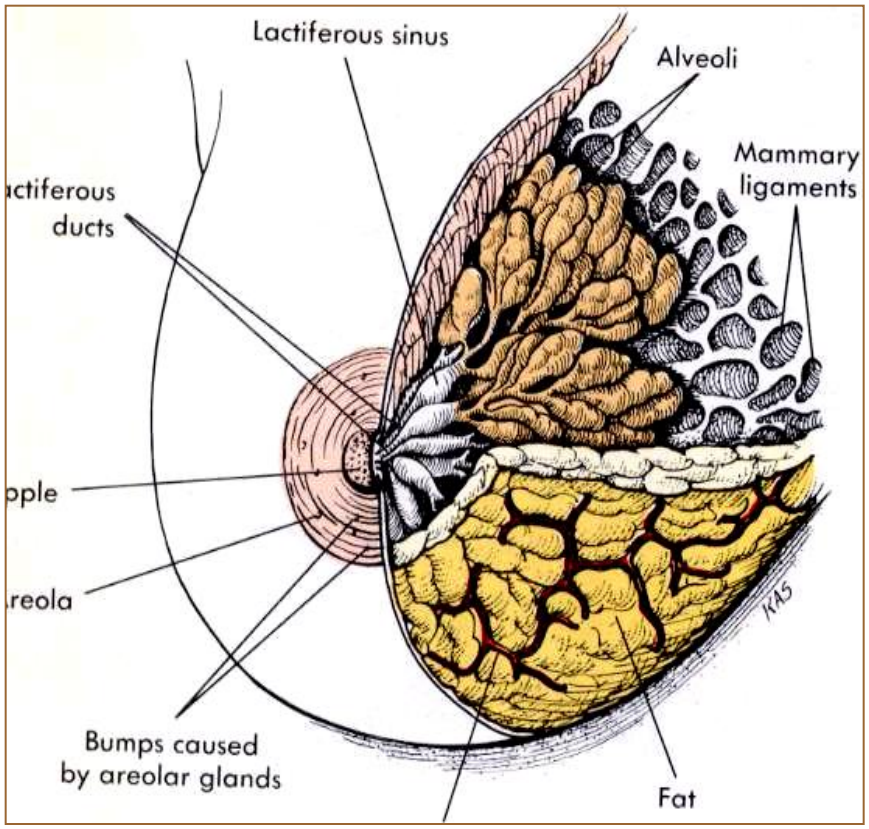
Fig. 28.17

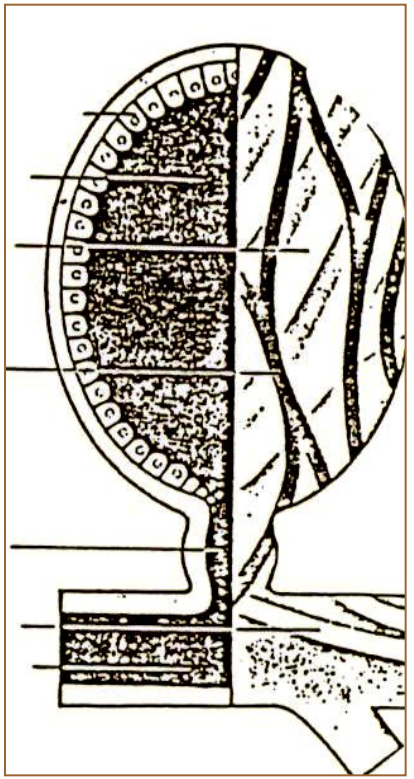
5.6.6 describe pregnancy-associated preparation for lactation & the roles of prolactin & oxytocin in supporting milk production & milk let-down

A. Hormonal Regulation of Breast Development:

During pregnancy:

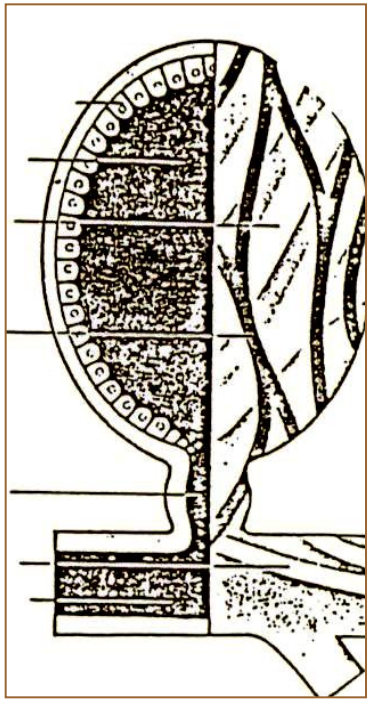
- **alveolus:** glandular structure involved in milk production; lined by a single layer of milk-secreting epithelial cells
- each mammary gland divided into 15-20 **lobes**; subdivided into **lobules**; basic component of each lobule is the **alveolus**

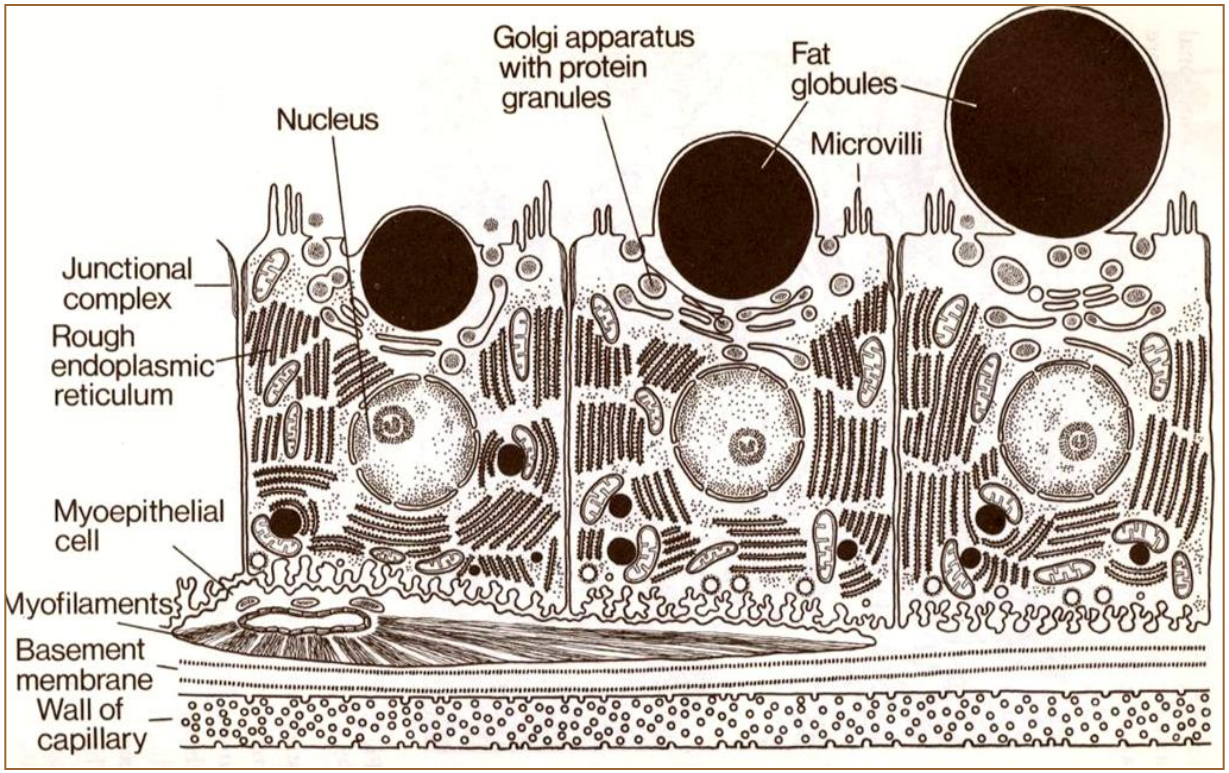




estradiol & **progesterone** levels increased during pregnancy ➢ stimulate further growth & development of alveoli & ducts
also **permissive** actions of **glucocorticoids**, **prolactin**, **human placental lactogen**

- **prolactin** stimulates milk **production**; actual **secretion** during pregnancy **inhibited** by high levels of _____ and _____





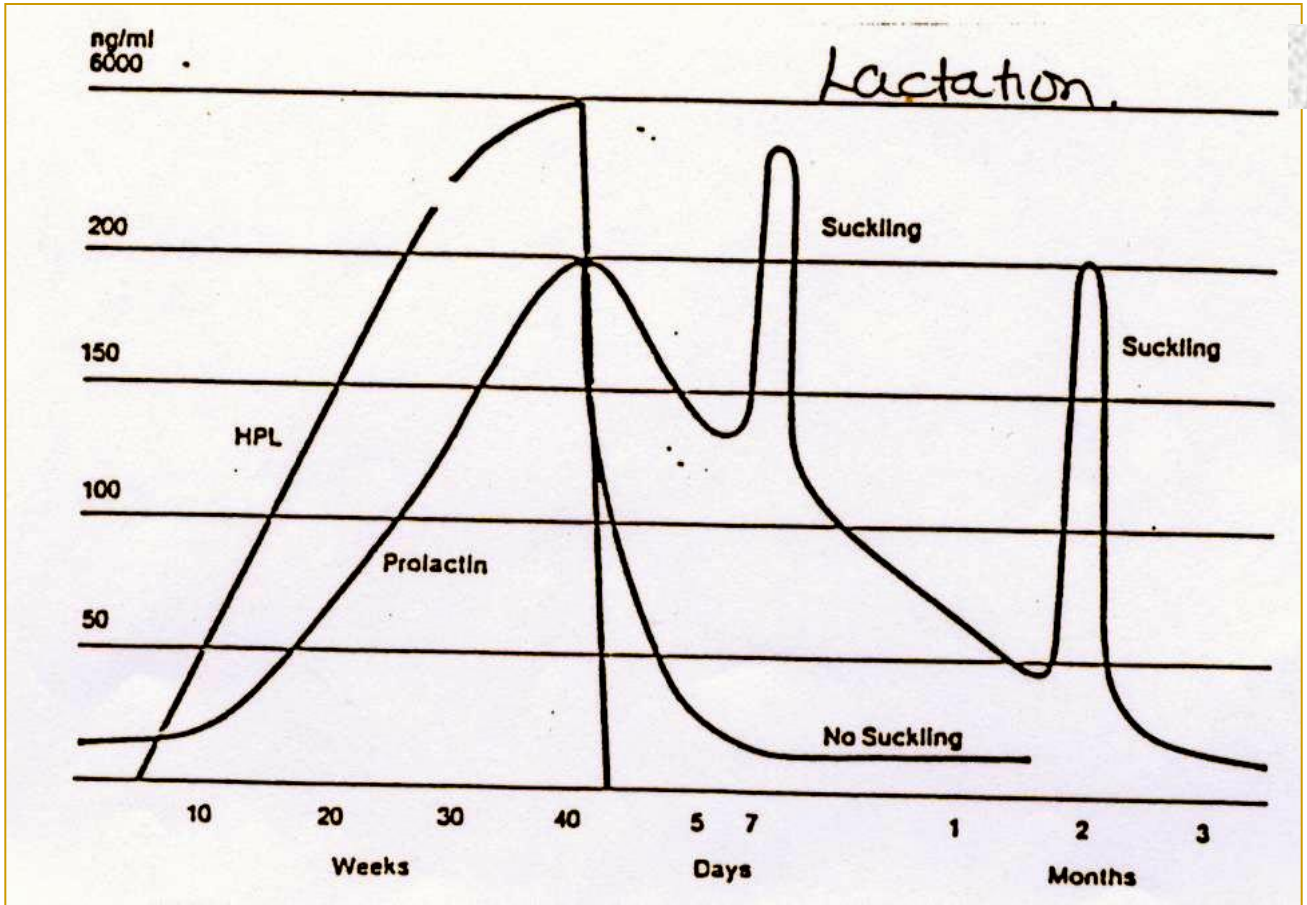
Postpartum:

levels of estradiol and progesterone ⇓⇓, allowing full expression of ????
now can have both **production** and **secretion**

1.6.7 explain how lactation is maintained

B. Classical Milk Let-down Reflex & Hormonal maintenance of Lactation

- 2 important hormones:
  - (i) **prolactin** ➔ secretion of casein, lactose, fatty acids
  - (ii) **oxytocin** ➔ contraction of myoepithelial cells
- both of these hormones required for continued lactation



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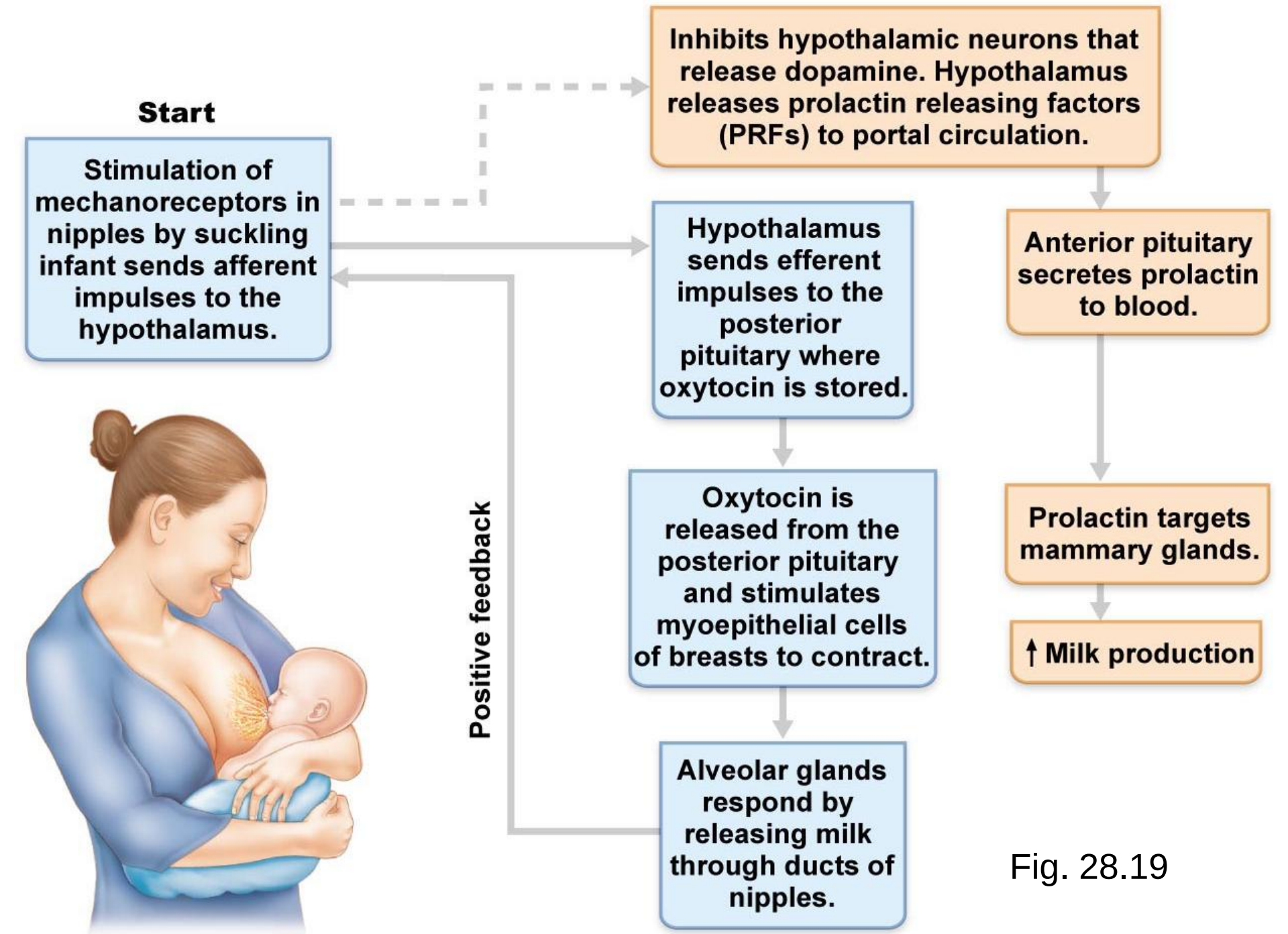
Start
Stimulation of mechanoreceptors in nipples by suckling infant sends afferent impulses to the hypothalamus.
Hypothalamus sends efferent impulses to the posterior pituitary where oxytocin is stored.
Oxytocin is released from the posterior pituitary and stimulates myoepithelial cells of breasts to contract.
Alveolar glands respond by releasing milk through ducts of nipples.
Positive feedback
Inhibits hypothalamic neurons that release dopamine. Hypothalamus releases prolactin releasing factors (PRFs) to portal circulation.
Anterior pituitary secretes prolactin to blood.
Prolactin targets mammary glands.
↑ Milk production

Fig. 28.19