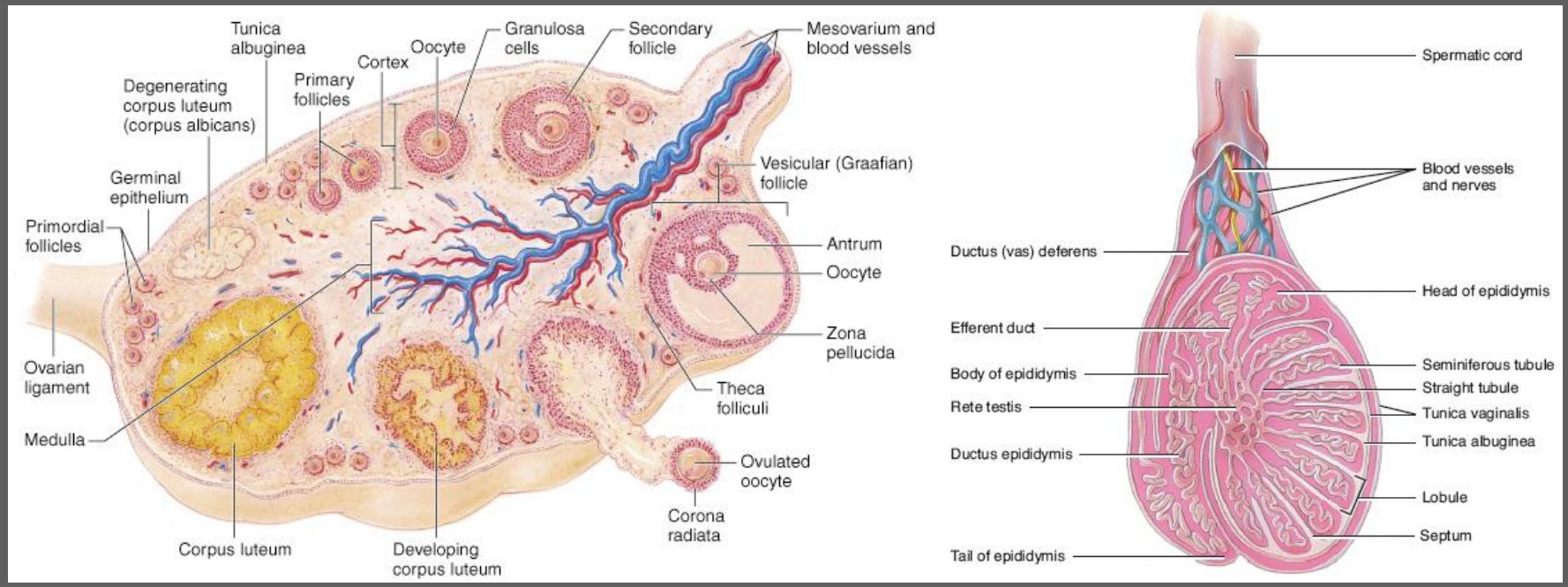
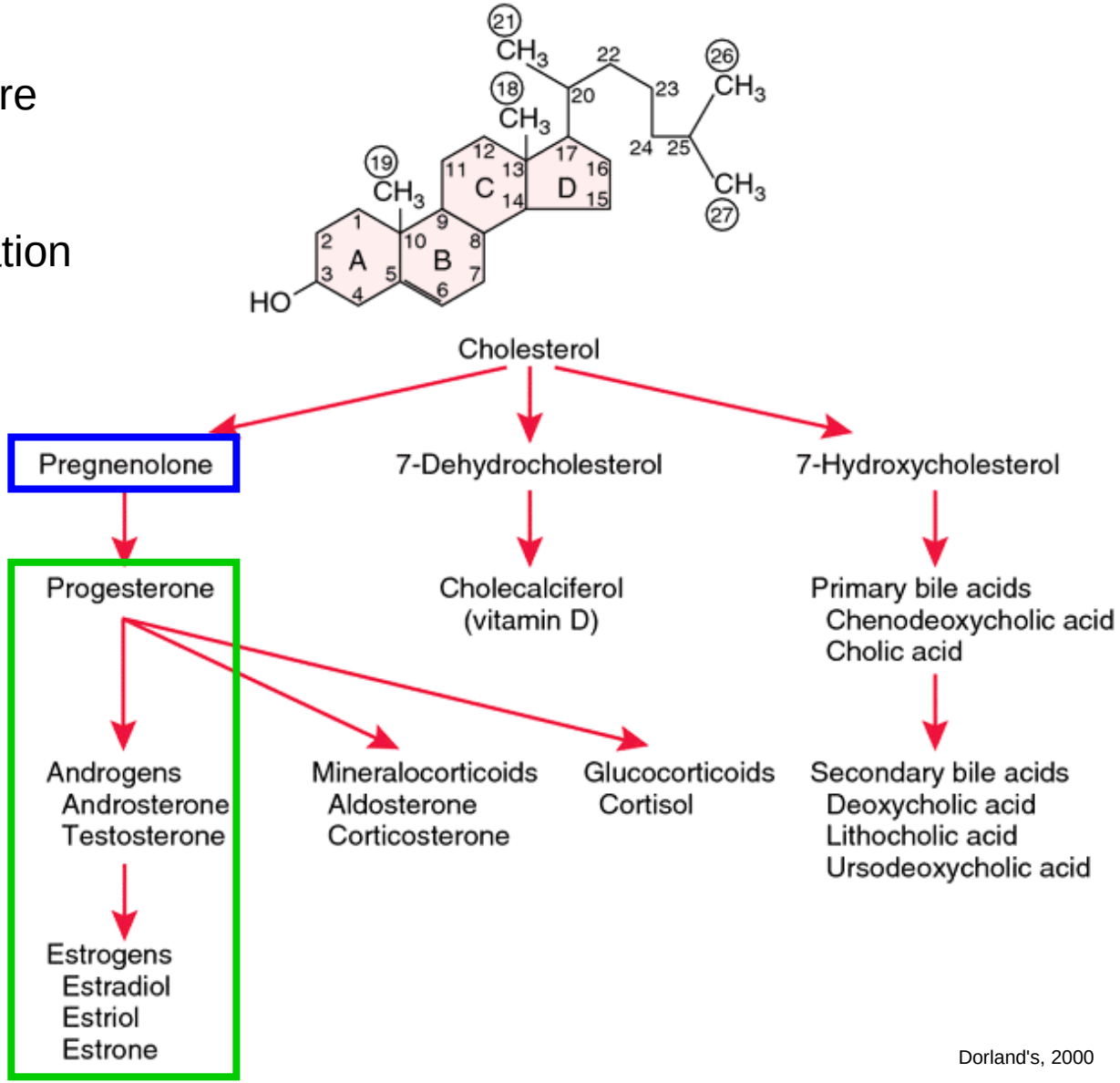
Gonads and hormones of the reproductive system



Steroid hormones

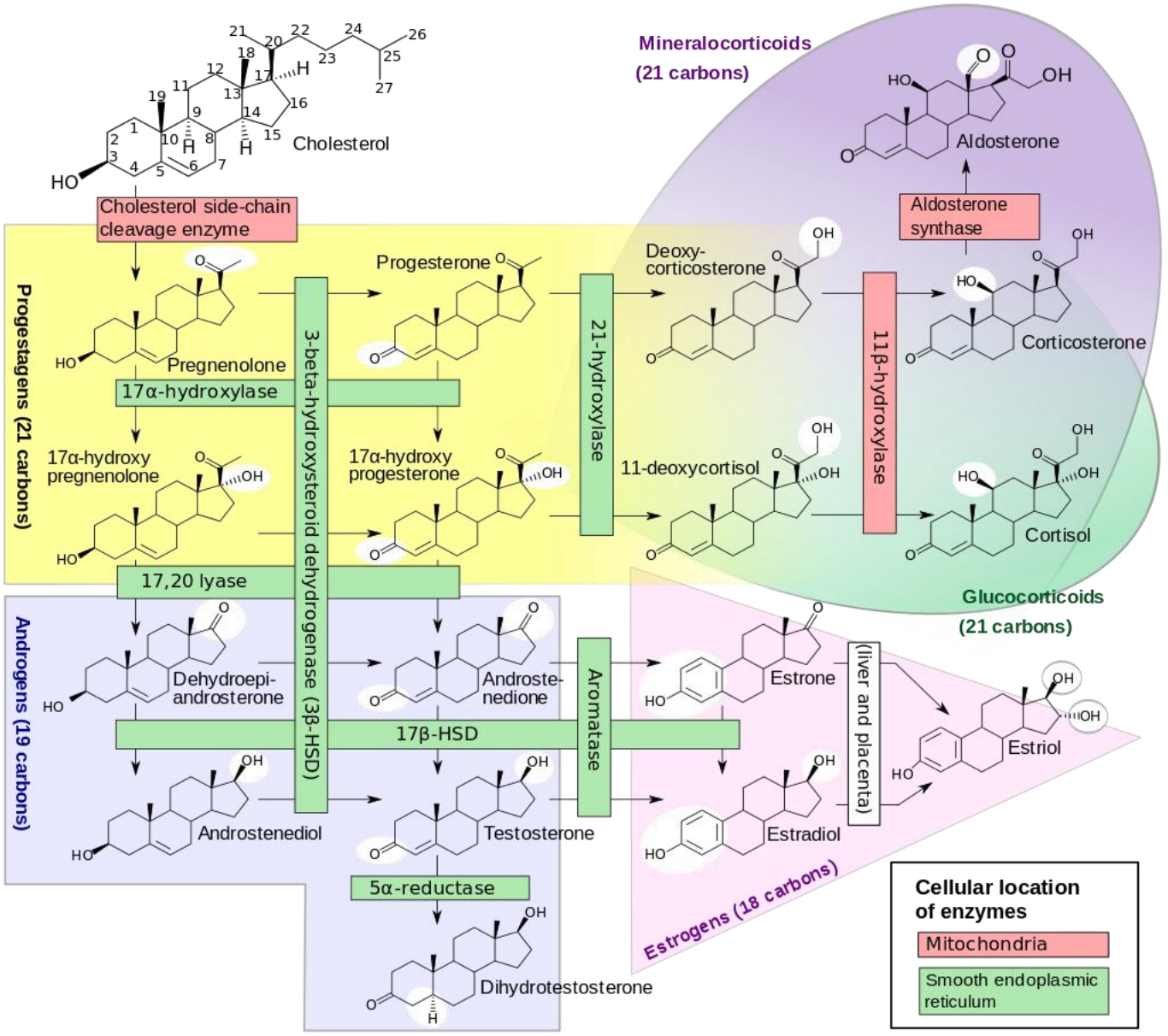
- derived from cholesterol
- differences in ring structure and side chains (*17-hydroxylase*)
- usually not stored (regulation at the level of synthesis)
- lipid soluble
- produced in the ovary, testes, placenta and adrenal glands



Steroid hormones

pregnenolone (21 C)
↓
progesterone
(**progestogens**, 21 C)
↓
androgens (19 C)
estrogens (18 C)

estron (E_1), estradiol (E_2), DHEA, testosterone, dihydrotestosterone and other effective hormones

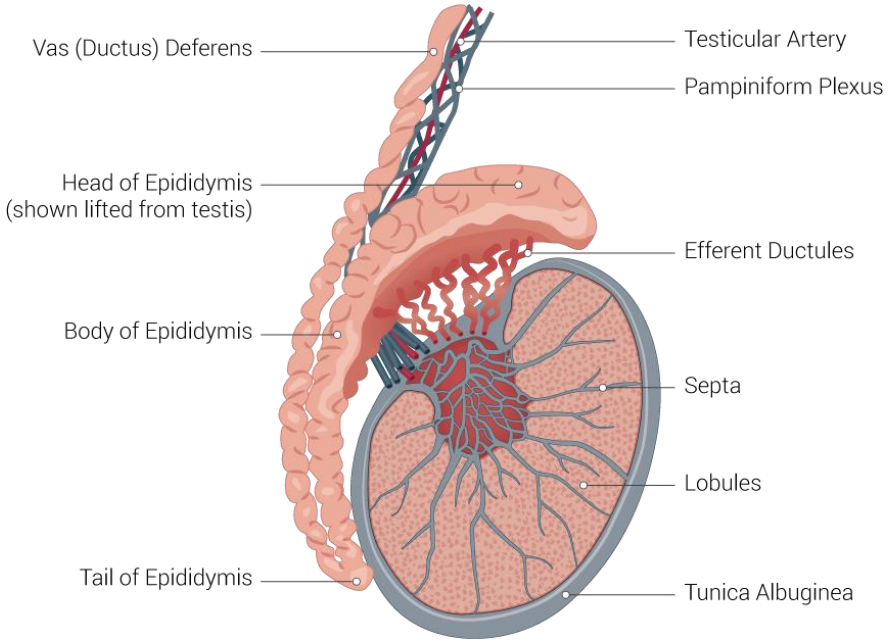


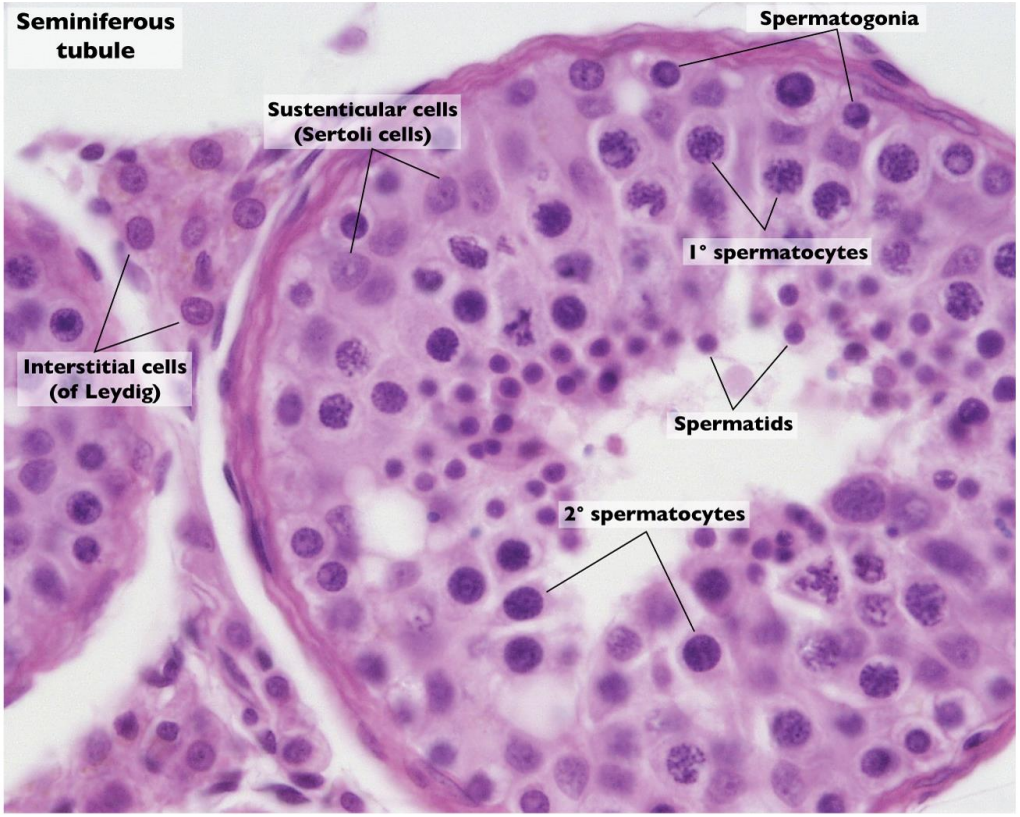
Regulation of sex hormones

- precursors for synthesis are present in all relevant glands
- presence of synthetic enzymes (hydroxylation of C17 > 17-ketosteroids)
- signal via receptors for superior **regulatory hormones** (hypothalamic-pituitary-gonads axis; eg FSH or LH)
- degraded in the liver (conjugation with OH groups to sulphates and glucuronic acid) and excreted in the bile or urine

Testicles (*testes*)

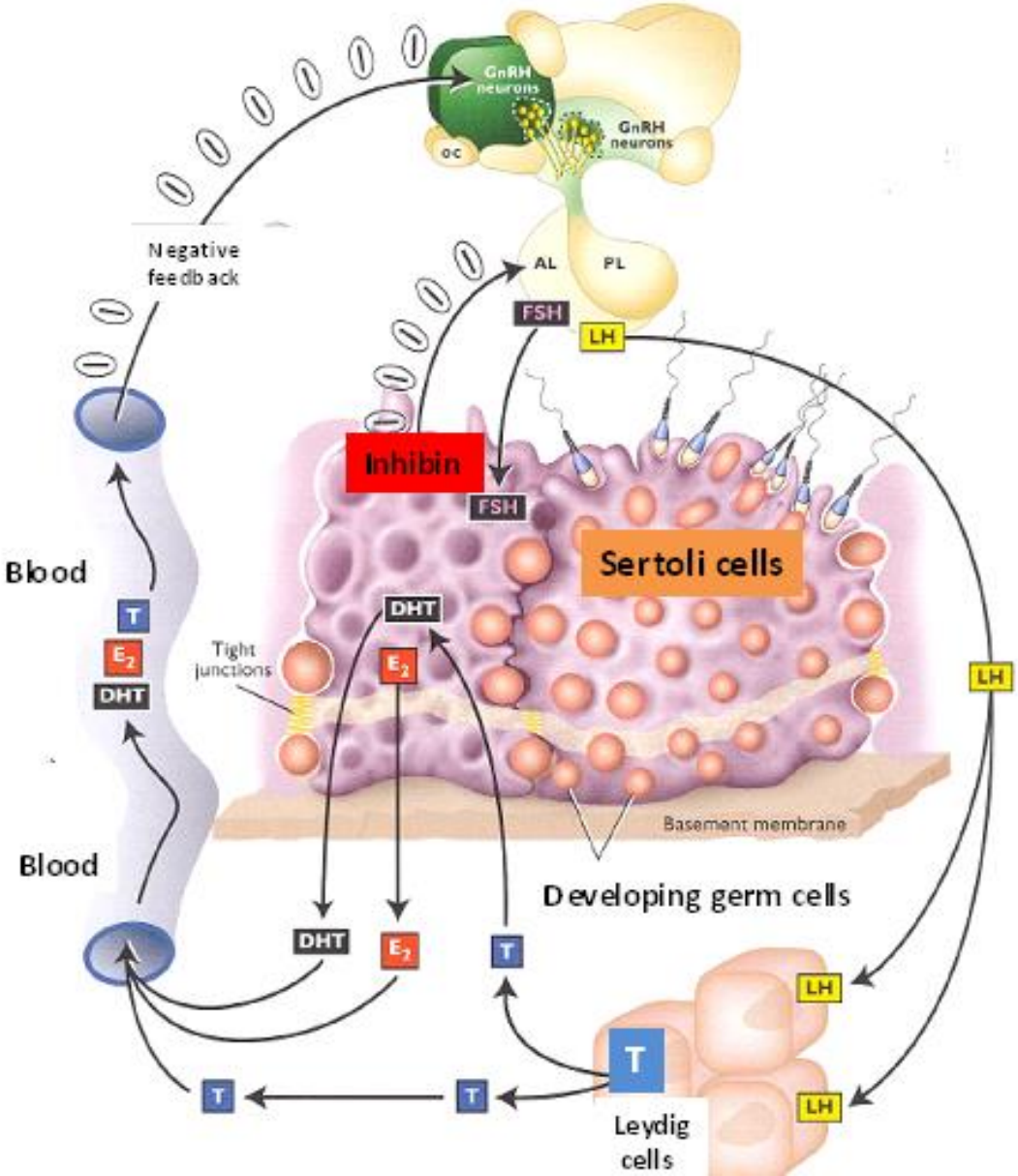
- parenchyma composed of seminiferous tubules, walls formed by germinal epithelium > spermatogenesis
- spermatogonia protected and sustained by **Sertoli cells** (produce **androgen transporter, inhibin and anti-Müllerian hormone**)
- interstitial cells located adjacent to the seminiferous tubules called **Leydig cells (testosterone production)**





Androgens

- steroid male sex hormones (19 C in the structure)
- **testosterone (T)**, 5α-dihydrotestosterone (DHT), 17-ketosteroids (dehydroepiandrosterone/DHEA and other molecules with weaker androgenic effects)
- DHT and estradiol (E_2) are formed from T in target cells and then released to plasma > DHT binds to T receptors; E_2 affects eg hypothalamus, pituitary gland or production of ejaculate)
- regulation via the hypothalamus (GnRH) and pituitary gland (FSH, LH)
- negative feedback (T, DHT, E_2)
- inhibin

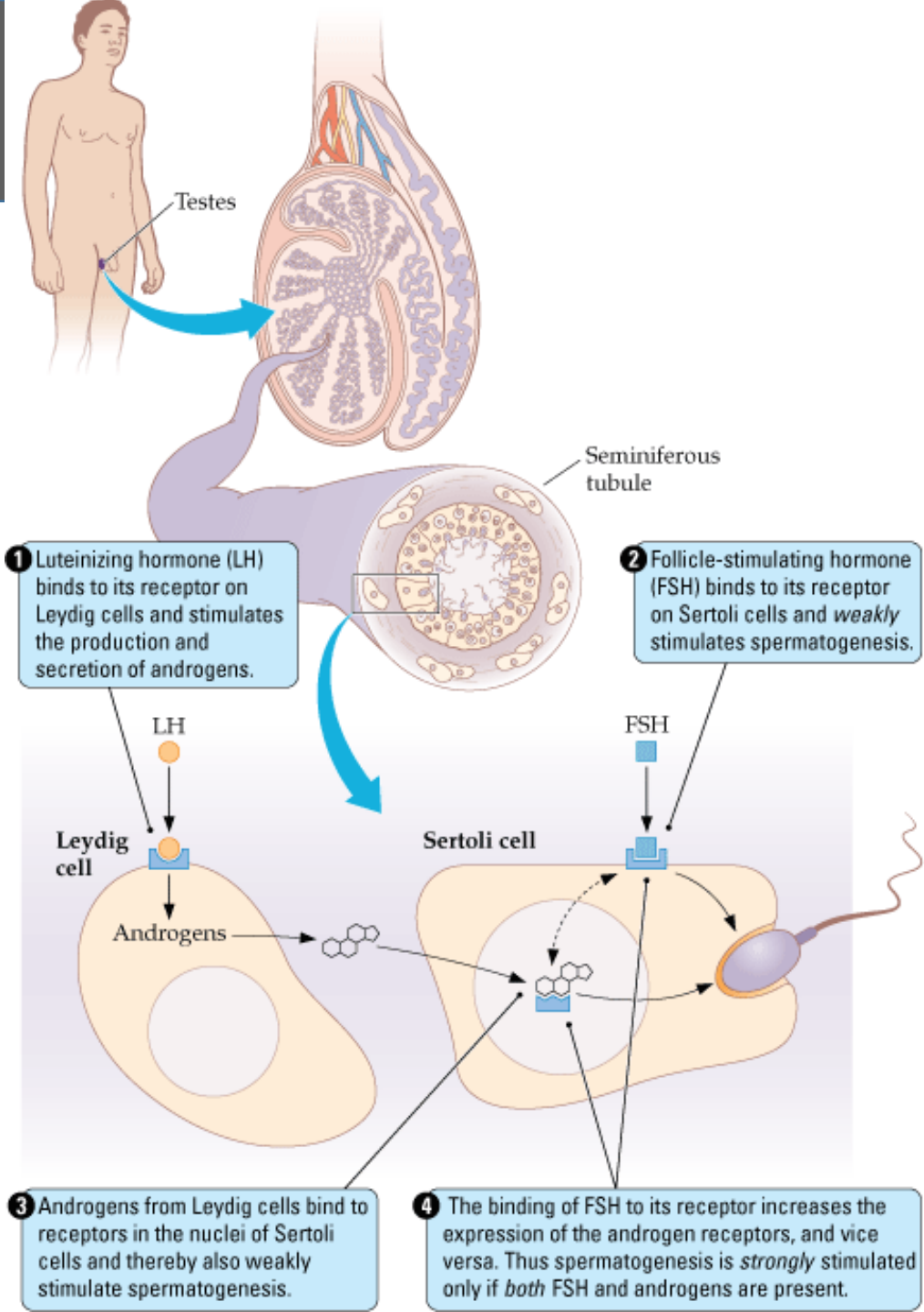


Androgens - testosterone (T)

- men: 95 % testosterone produced in testes + 5 % produced in adrenal cortex
- women: ovaries and adrenal cortex
- Leydig cells stimulated by **FSH** (increases expression of **LH receptor**) and **LH** (induces the synthesis of **T**)
- Sertoli cells stimulated by **FSH** > synthesis of **androgen binding protein** (T transport) and inhibin (regulation of endocrine production)
- plasma concentrations 15 times higher in men than in women (decreases with age)
- protein-bound transport (98 % albumin and sex hormone binding globulin)
- the testicles are target organ for T > the seminiferous tubules are protected by hematotesticular barrier > T must be bound to the androgen-binding protein to get across the barrier!

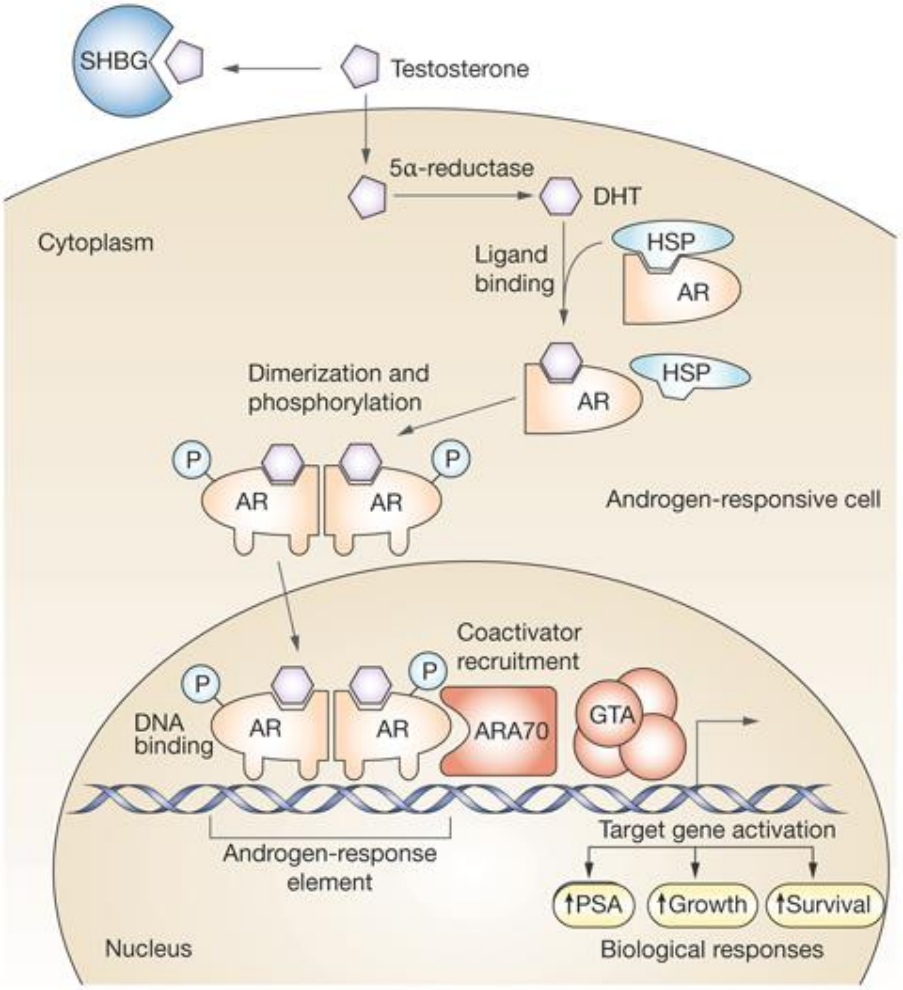
Androgens - function

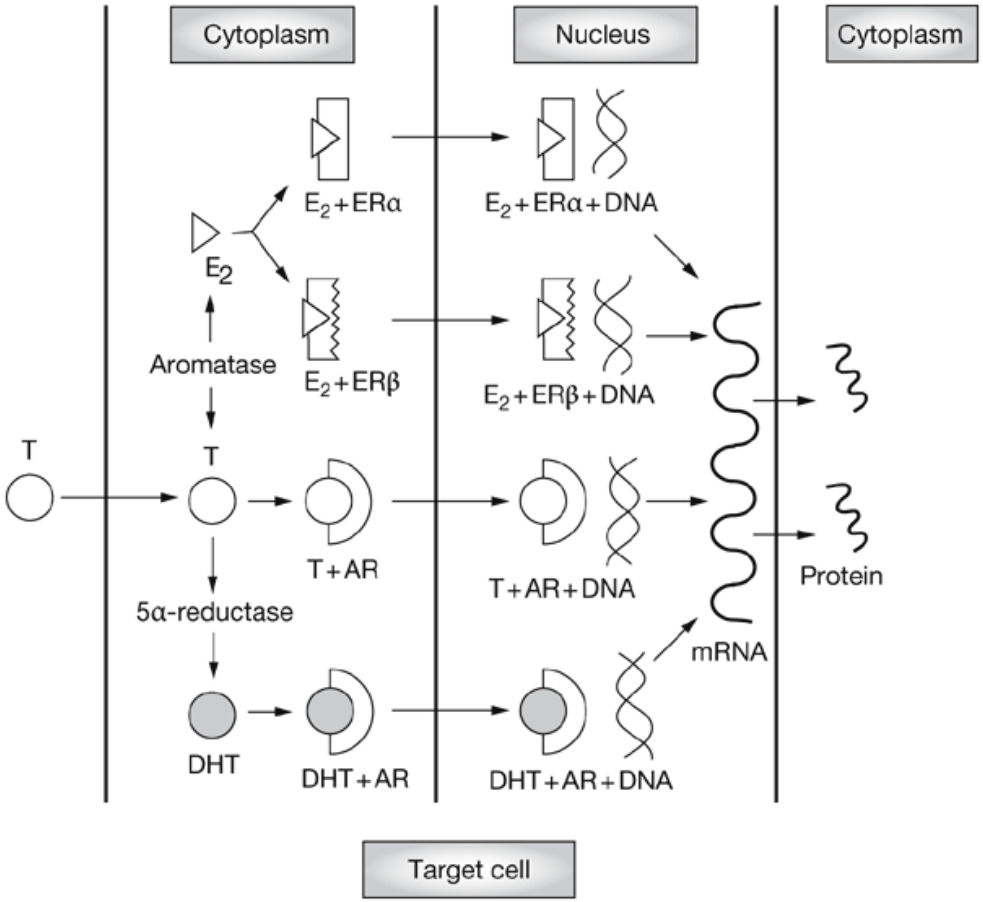
- spermatogenesis (paracrine)
- male gender differentiation in the prenatal period
- development of male secondary sex characteristics
- growth and function of the genitals, prostate and seminal vesicles
- stimulating effect on hematopoiesis
- anabolic effects
- libido, potency, ability to have sex
- influencing behaviour by affecting CNS (e.g. aggression)



Androgens - mechanism of action

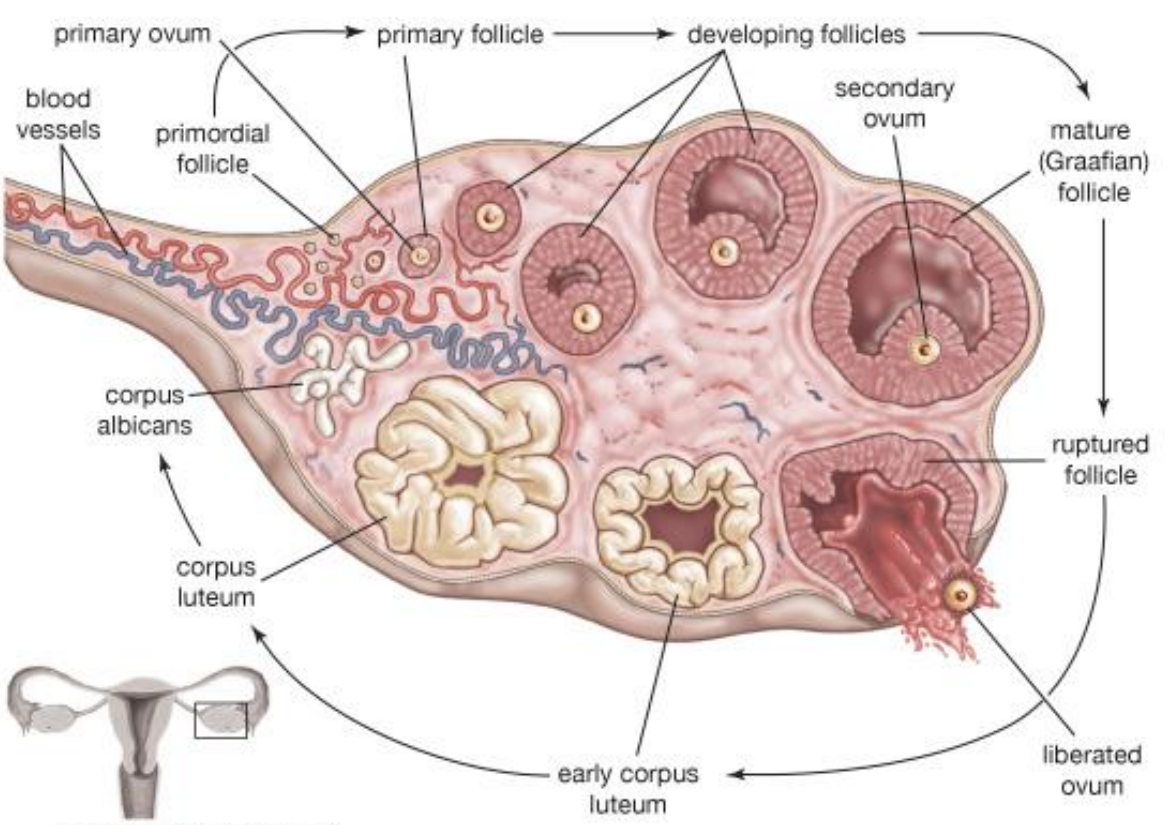
- binding to nuclear androgen receptors (directly **T** or after converting to **DHT**)
- conversion to **estradiol** (aromatase) and estrogen receptor activation
- dimer formation and translocation to the nucleus > influencing gene expression

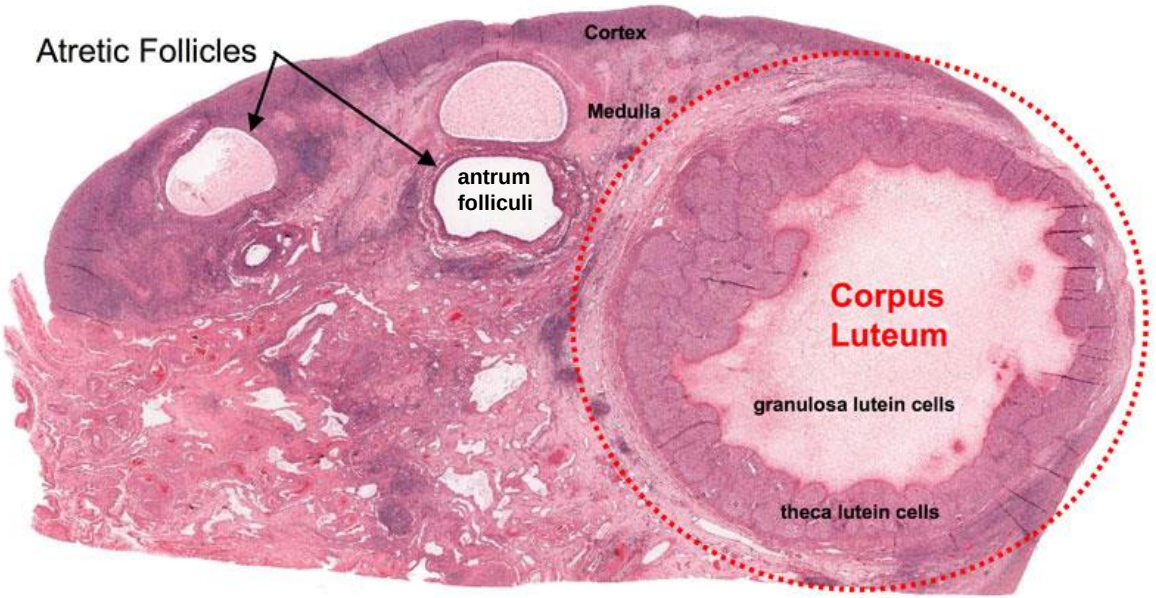




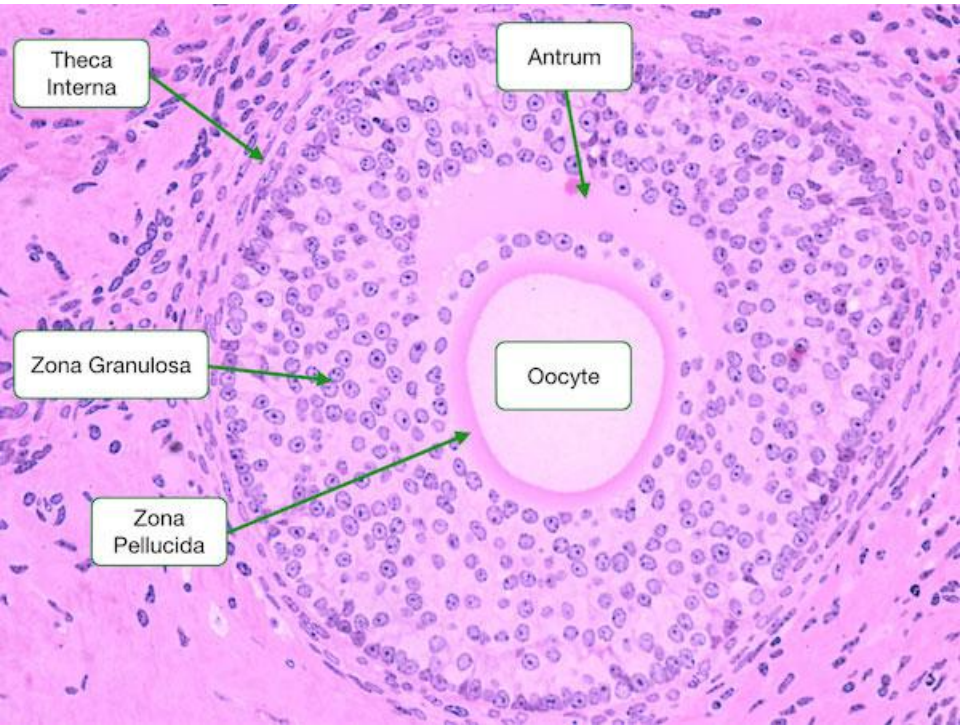
Ovaries

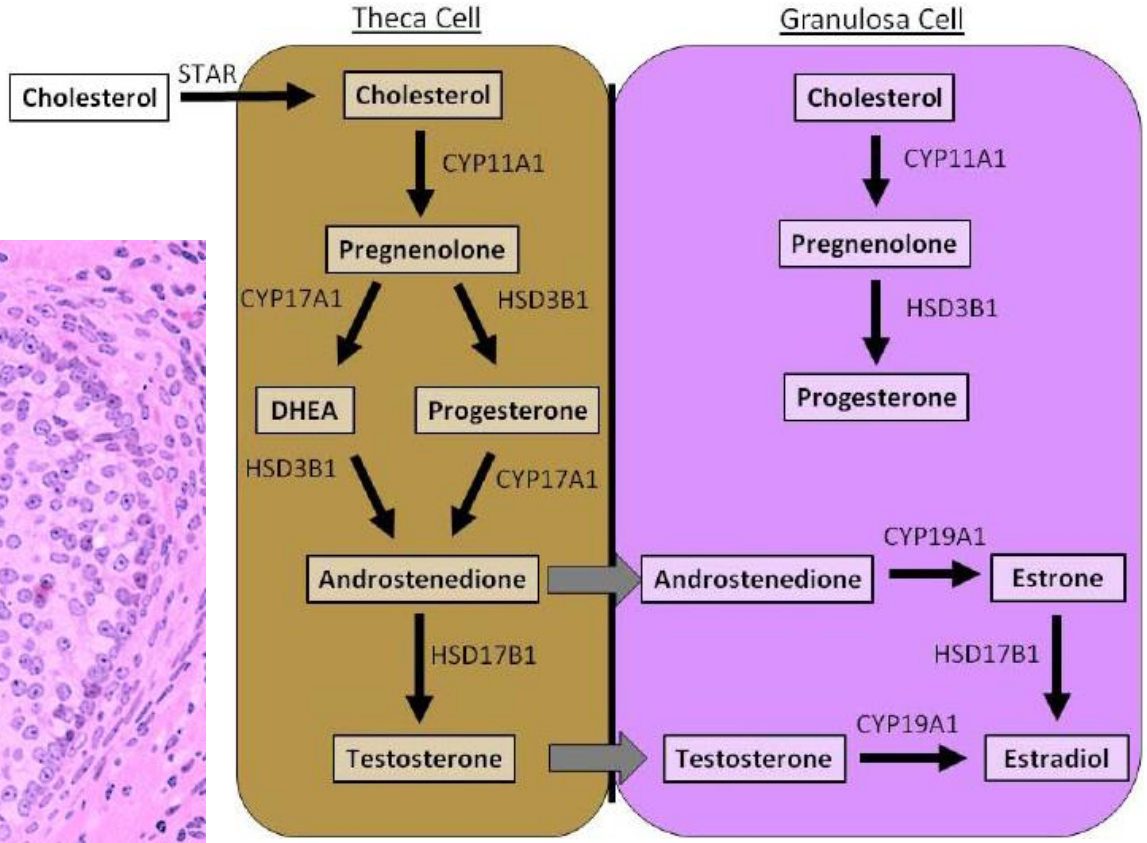
- epithelium covering the surface
- ligament *tunica albuginea*
- cortex (**contains follicles**)
- medulla (connective tissue with blood vessels and nerves)
- follicles (oocyte + follicular cells)
- layer of follicular cells and ligaments *theca folliculi* (**steroids, inhibin**)
- humans about 400 thousand of follicles; 400–450 ruptures
- primordial > primary > secondary > Graafian f.
- corpus luteum (**estrogens, progesterone**)





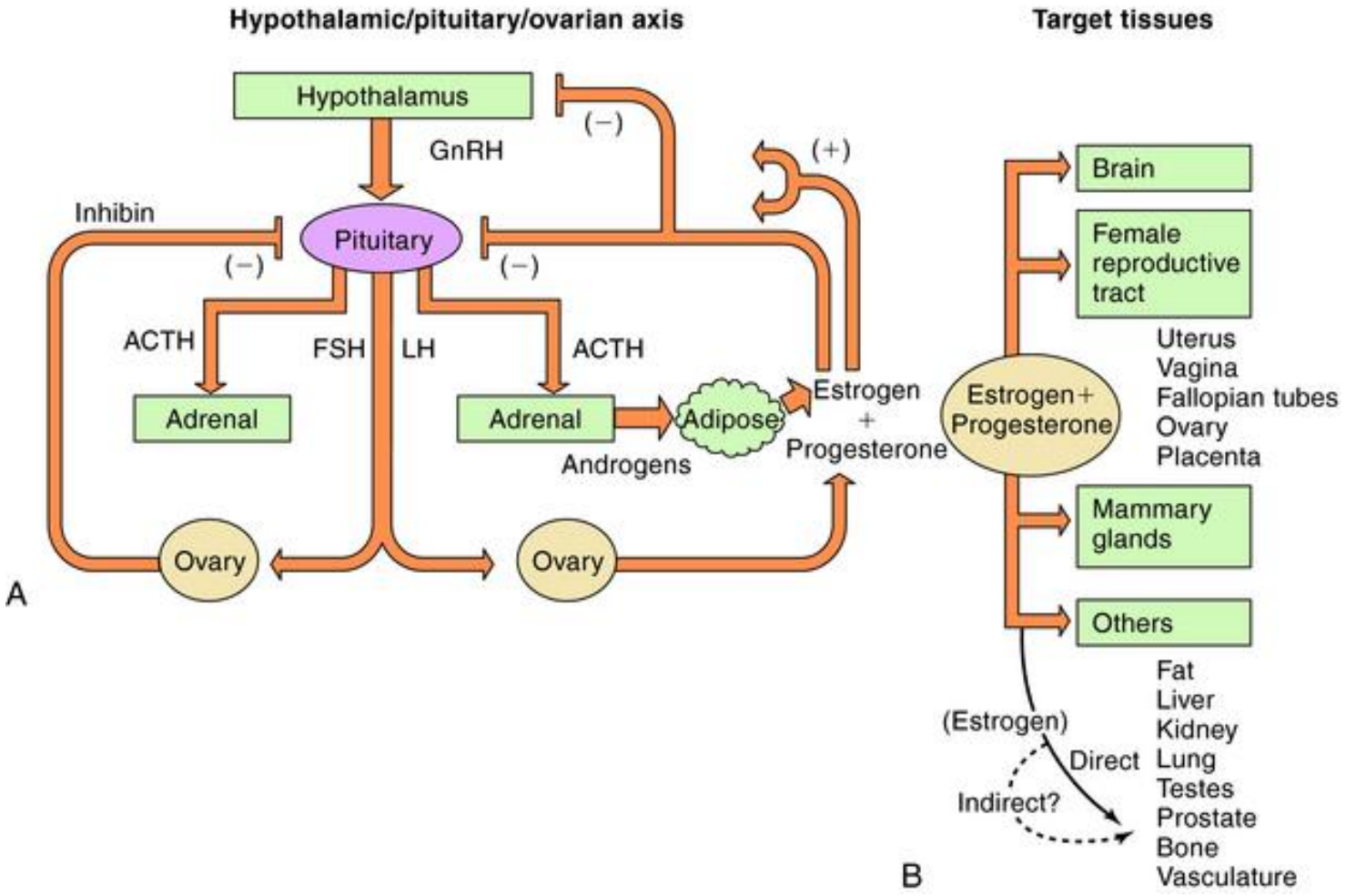
Ovaries - structure of follicles





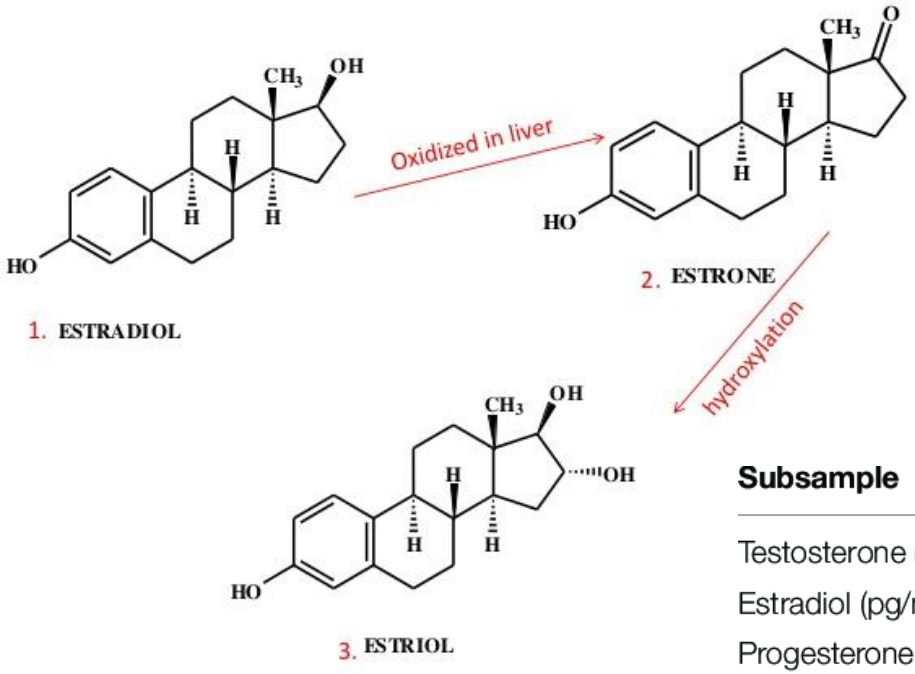
Ovaries - regulation of hormonal activity

- hypothalamic-pituitary-ovarian axis
- negative feedback



Estrogens

- sex hormones belonging to steroids (18 C in the structure)
- synthesized from 17-ketosteroid androstenedione and partly from testosterone
- granulosa and theca (produces androgens > granulosa) cells in the ovaries, placenta, adrenal cortex, Leydig cells, some target cells of testosterone
- **estradiol (E_2)**,**estron (E_1)** and **estriol (E_3)**
- relative efficiency $E_2 : E_1 : E_3$ is 10 : 5 : 1
- transported by the blood mainly in complex with sex hormone binding globulin
- degraded mainly in the form of estriol



Subsample	Men (*n* = 54)	women NC (*n* = 51)	*F*	*p*
Testosterone (pg/ml)	113.57 ± 62.45	43.96 ± 18.63	56.69	< 0.001
Estradiol (pg/ml)	2.40 ± 0.73	2.90 ± 1.00	8.37	0.005
Progesterone (pg/ml)	52.52 ± 53.67	153.75 ± 139.71	24.12	< 0.001

Estrogens - function

- typical sexual behavior of females (estrus)
- **stimulate the formation of secondary sex characteristics** during puberty (breast growth, vaginal changes, subcutaneous fat distribution, hip growth) + cooperation with androgens (pubic hair grow)
- **stimulate uterine mucosa proliferation and uterine muscle contractions** (increased sensitivity to oxytocin)
- thickening of vaginal mucosa and increased losses of epithelial cells (glycogen from them is processed by bacteria to produce lactic acid > decreased pH and lower risk of infections)
- during the menstrual cycle **stimulate the maturation of follicles in the ovaries**
- regulate oocyte progression through the fallopian tube and prepare it for sperm penetration (regulation of fertilization)
- changes the consistency of the cervical mucus plug (support of sperm movement and survival during ovulation)
- increase blood clotting
- affect water management (local and renal retention > edema)
- inhibits bone growth in length, speed up closure of epiphyseal crevices, stimulate osteoblasts; reduce LDL levels and increase VLDL and HDL
- affect the CNS (sexual and social behavior etc.)

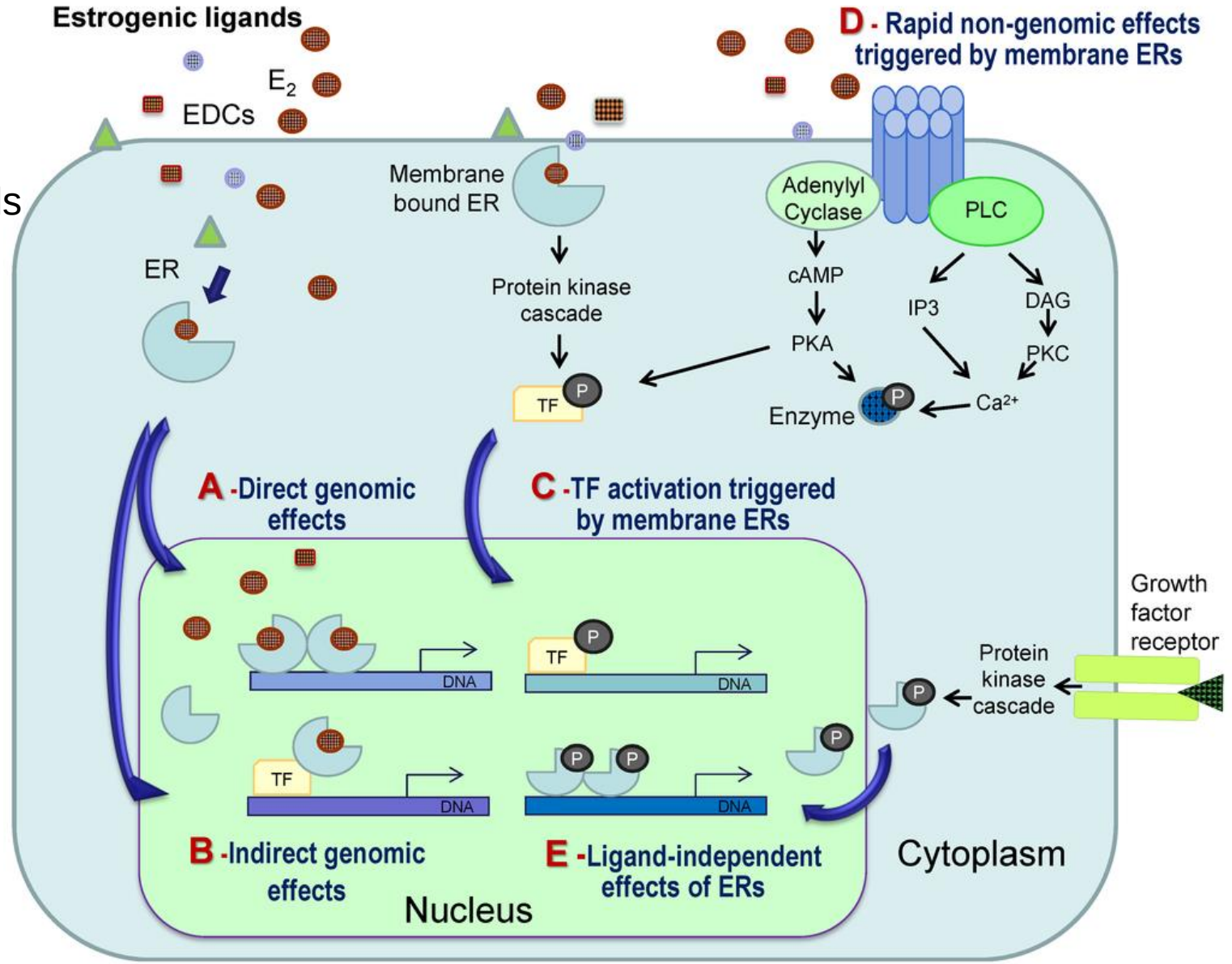
Estrogens - mechanism of action

ERα

- uterus
- vagina
- blood vessels
- breasts

ERβ

- ovaries
- prostate



Progestogens / progestins - progesterone

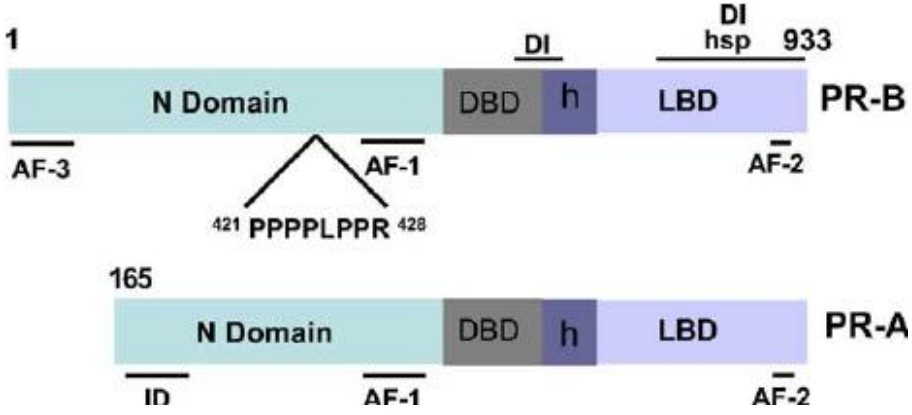
- synthesis from pregnenolone; 21 C in structure
- **corpus luteum**, ovarian follicles, placenta, adrenal cortex (also in men)
- transported in plasma bound to albumin and globulin transcortin
- the major degradation product of progesterone is pregnanediol (liver)
- often antagonistic action with estrogens (necessary previous or current effect of estrogens)

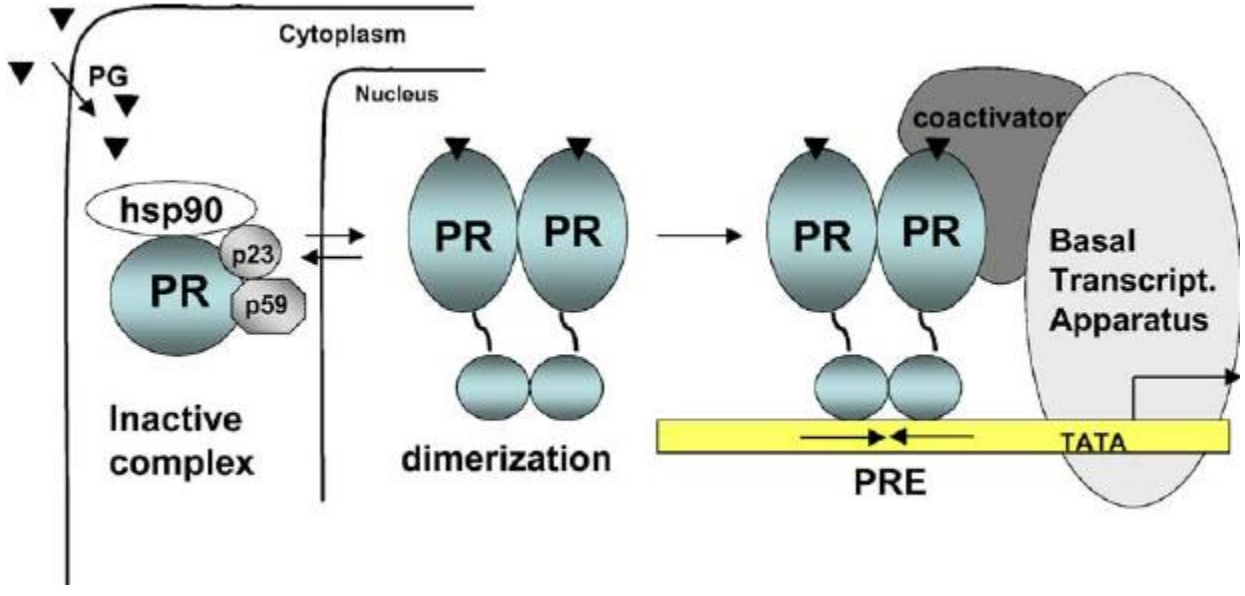
Function:

- **preparing a woman's genitals for receiving and maturing a fertilized oocyte and maintaining pregnancy**
- **after exposure to E, stimulates growth myometrial and endometrial growth and remodeling** (gland remodeling, change in vascularity and glycogen content) = transition from proliferative to secretory phase
- support nidation of fertilized oocyte, reduces activity of myometry
- reduces the external uterine cervix and changes the consistency of the mucus plug (impermeability to sperm)
- in luteal phase inhibits the release of LH
- increase of basal temperature (thermogenic effect)

Progesterone - mechanism of action

- nuclear (nPR) and membrane (mPR) progesterone receptors
- isoforms A and B



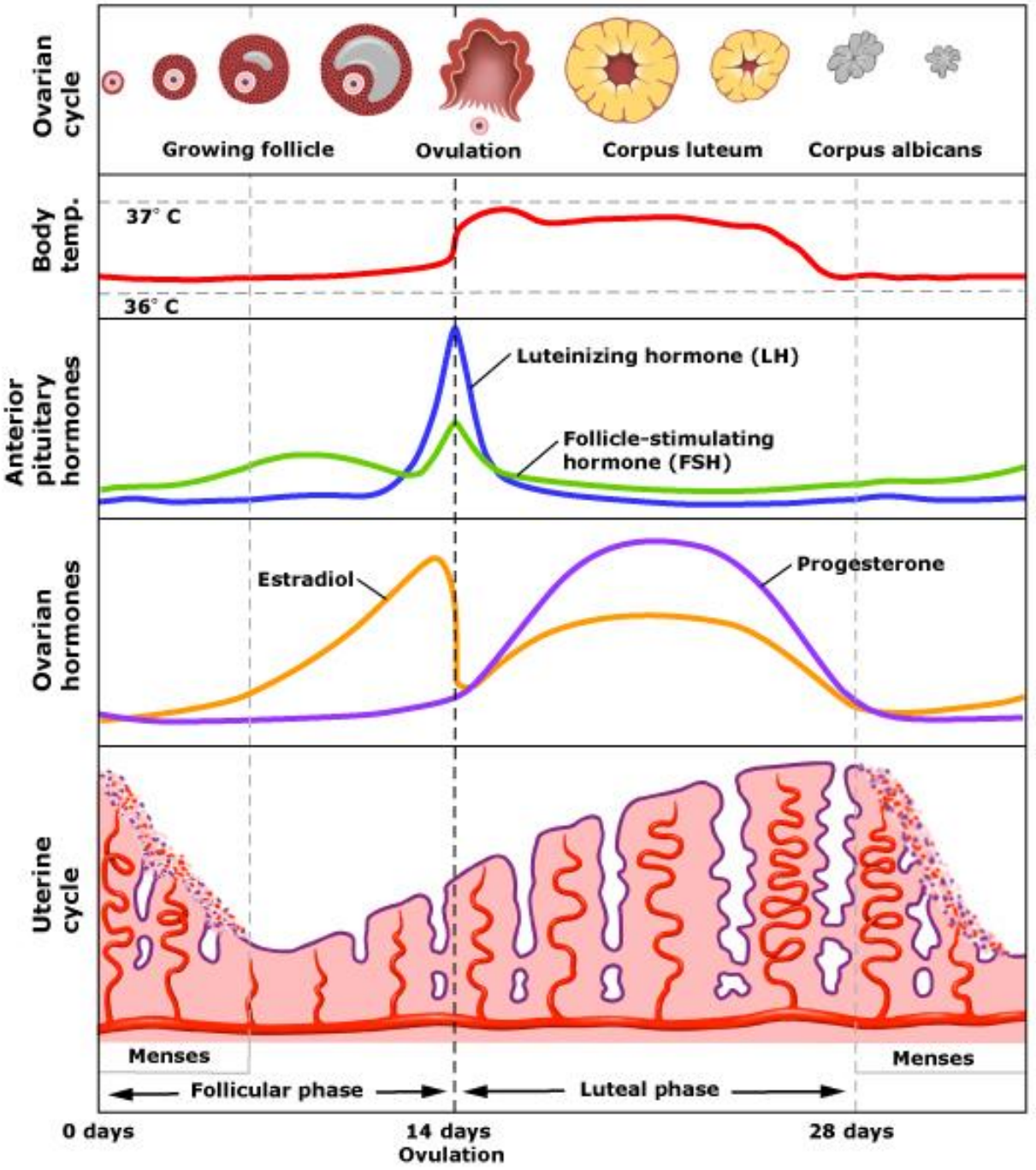


Menstrual cycle

- approx. 28-day secretion:

Gonadotropin-releasing hormone (GnRH)
Dopamine (PIT)
Follicle-stimulating (FSH)
Luteinizing (LH)
Prolactin (PRL)
Progesterone (P)
Estrogens (E)
Inhibin

- preparing one egg for fertilization, the female genitals for receiving sperm and nidating oocyte
- follicular / proliferative phase, ovulation, luteal / secretory phase

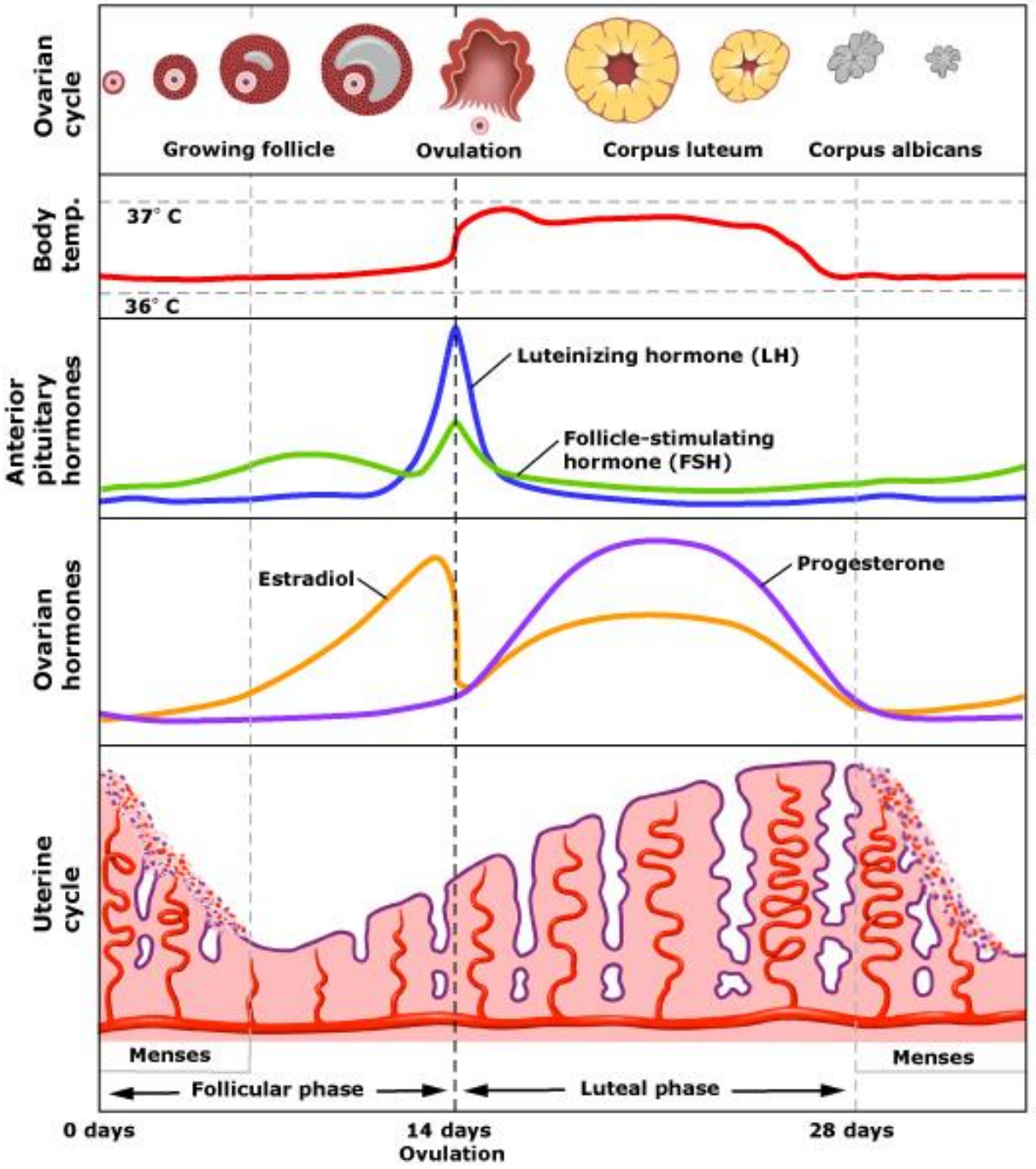


Menstrual cycle

- bleeding (1st day of the cycle)

Proliferation / follicular phase:

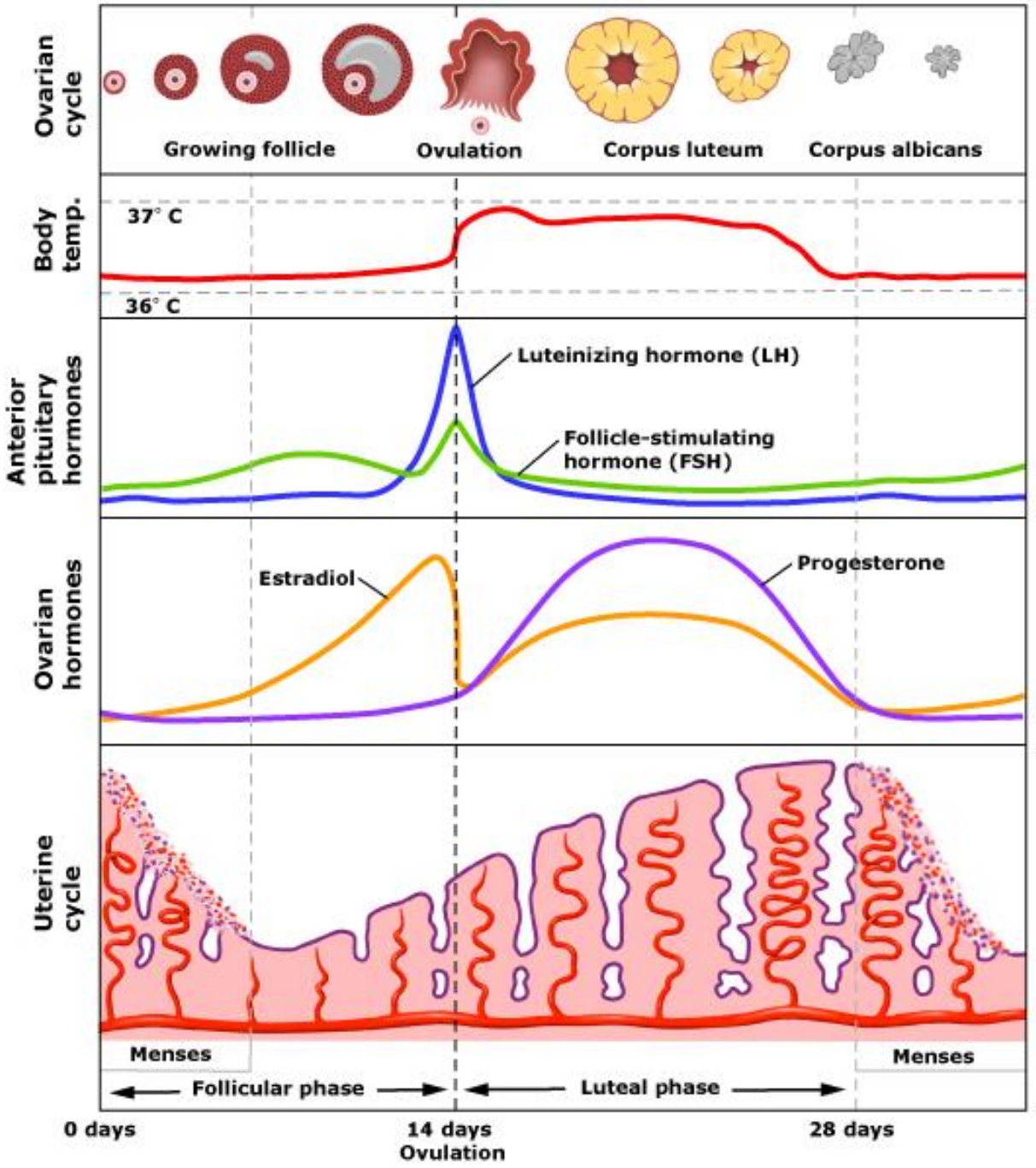
- endometrial growth and renewal
- under the influence of **FSH** matures about 20 follicles > one becomes dominant and increases production of **estrogens** > **E_2 has a positive feedback effect** on adenohypophysis and the production of FSH and LH > stimulation of **LH** synthesis and release > **ovulation**



Menstrual cycle

Secretory / luteal phase:

- increased mucosal secretion and lower myometrial contractility, preparation for nidation
- corpus luteum develops > **progesterone** production > **P and E_2 dampens production of GnRH** and thus also **LH and FSH** (negative feedback of E_2) > without fertilization and nidation, CL decays the 22nd day of the cycle >**decrease of P and E concentrations** > vascular constriction and endometrial ischemia



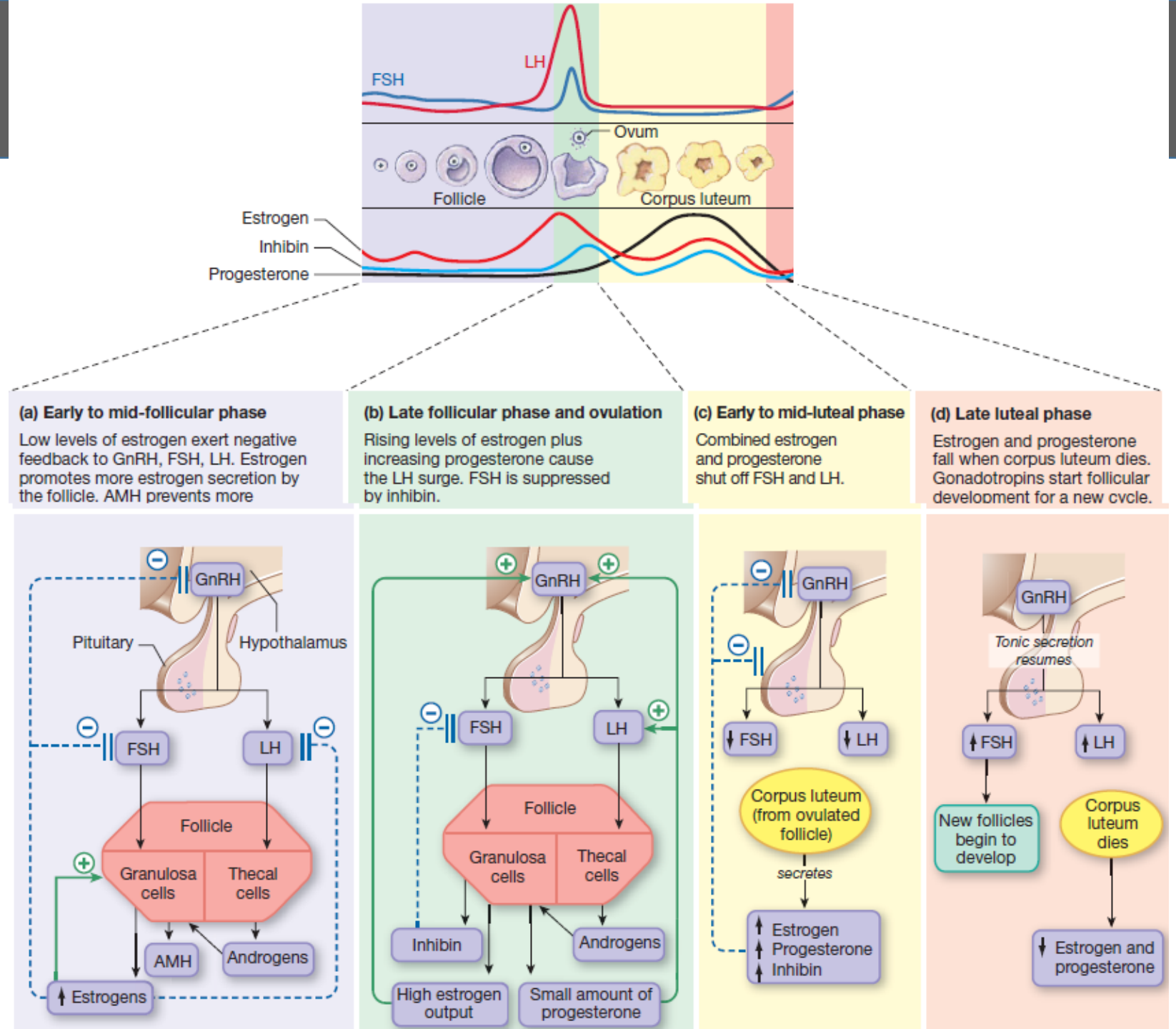
Menstrual cycle - hormonal regulation

Follicular phase:

- low LH levels promote androgen production in thecal cells and FSH induces aromatase in granulosa cells that forms estrogens from androgens synthesized in theca
- estrogens increase the density of FSH receptors in the follicle (formation of a dominant follicle)
- at the beginning of the follicular phase estrogens create **negative feedback** and suppress FSH and LH (indirect effect on GnRH)
- in the late follicular phase, estrogens increase the amount of LH receptor in granulosa cells > progesterone and its conversion to other androgens in theca > more estrogens
- inhibin suppresses FSH
- estrogens increase LH secretion (**positive feedback**) > LH-peak > **ovulation**

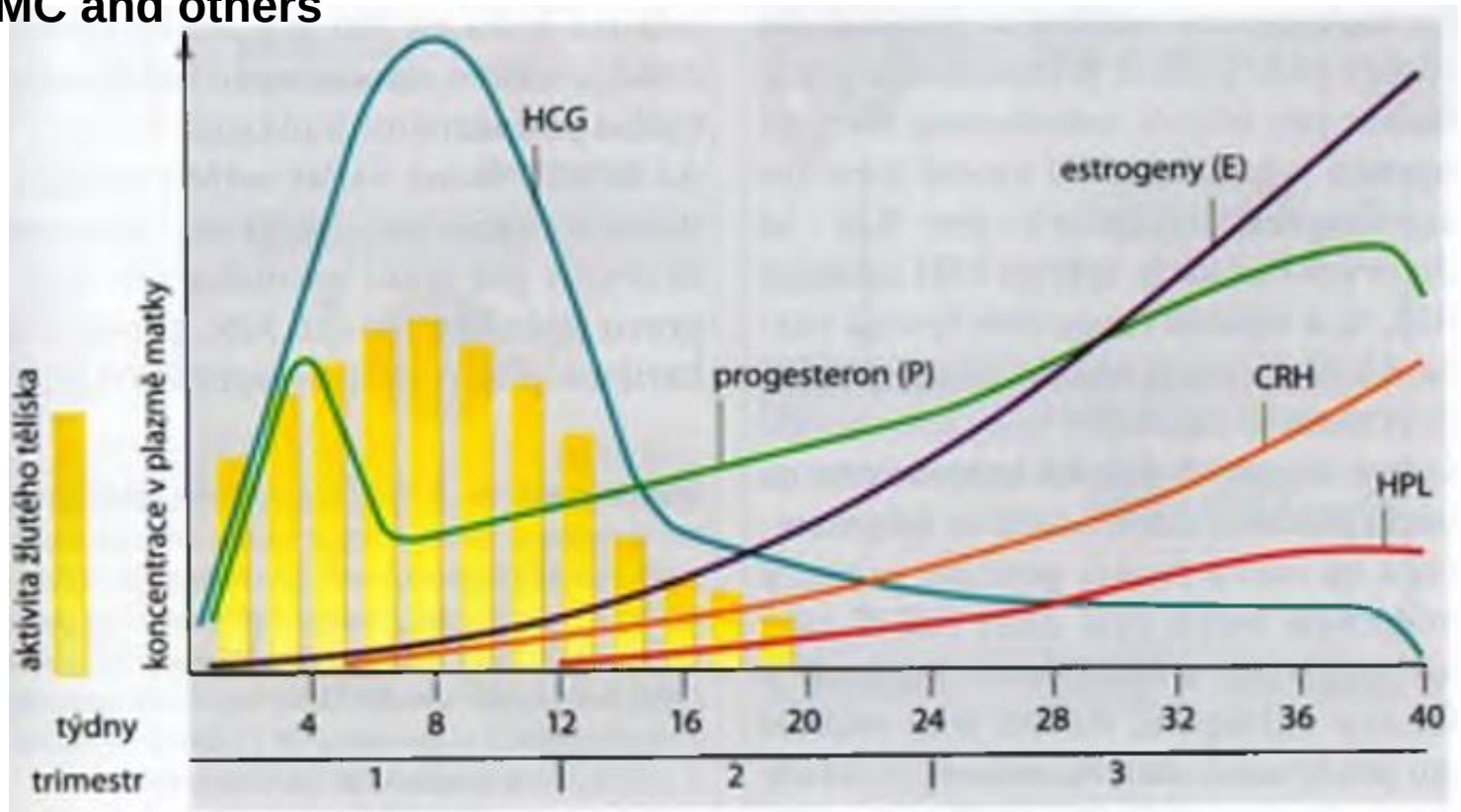
Luteal phase:

- LH, FSH and estrogens turn follicle into corpus luteum > significant increase in progesterone > P and E suppress secretion of GnRH, LH and FSH (**negative feedback**) > decrease in P and E > resumption of FSH secretion


FSH
LH
Ovum
Follicle
Corpus luteum
Estrogen
Inhibin
Progesterone
(a) Early to mid-follicular phase
Low levels of estrogen exert negative feedback to GnRH, FSH, LH. Estrogen promotes more estrogen secretion by the follicle. AMH prevents more
(b) Late follicular phase and ovulation
Rising levels of estrogen plus increasing progesterone cause the LH surge. FSH is suppressed by inhibin.
(c) Early to mid-luteal phase
Combined estrogen and progesterone shut off FSH and LH.
(d) Late luteal phase
Estrogen and progesterone fall when corpus luteum dies. Gonadotropins start follicular development for a new cycle.
GnRH
Pituitary
Hypothalamus
FSH
LH
Follicle
Granulosa cells
Thecal cells
AMH
Androgens
Estrogens
Inhibin
High estrogen output
Small amount of progesterone
Corpus luteum (from ovulated follicle)
secretes
Estrogen
Progesterone
Inhibin
Tonic secretion resumes
New follicles begin to develop
Corpus luteum dies
Estrogen and progesterone

Hormonal regulation of pregnancy

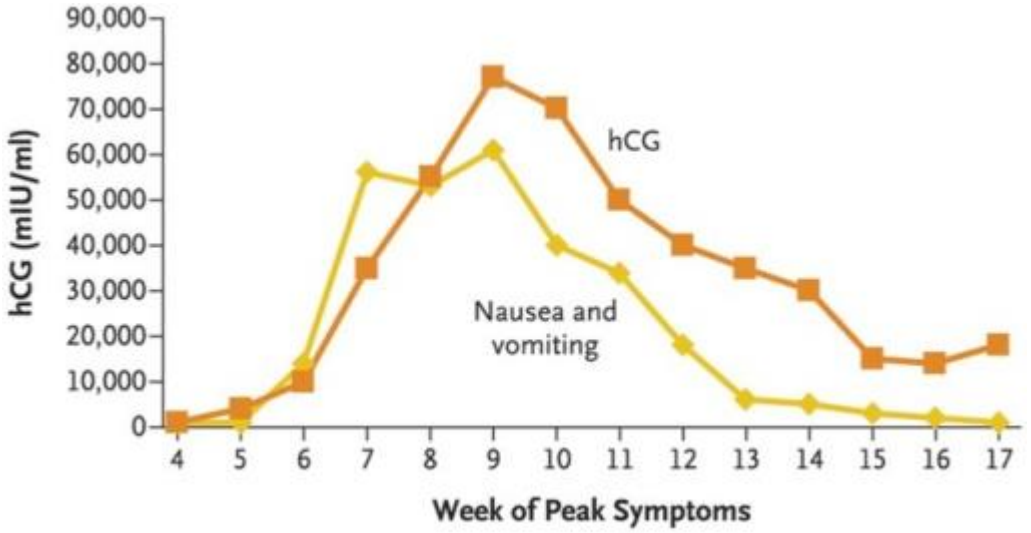
- mother's ovarian hormones > placental hormones protect corpus luteum
- placental hormones enter the circulation of fetus and mother
- placenta needs steroid precursors from adrenal cortex of mother and fetus > produce **P and E** > DHEA in adrenal cortex > E/T in the placenta/testes
- **human chorionic gonadotropin (HCG), corticotropin-releasing h. (CRH), estrogens (E), progesterone (P), human placental lactogen (HPL), POMC and others**



Hormonal regulation of pregnancy: Human chorionic gonadotropin (HCG)

- produced in placenta from day 10 of pregnancy (pregnancy tests from urine)
- 237 AA, heterodimer (α subunit identical to LH, FSH and TSH)
- acts through the hHCG receptor and cAMP
- significant action in the first trimester
- **replaces the action of LH and maintains the production of P and E in corpus luteum** (produced mainly by placenta from week 6), which keep the endometrium in the secretory phase
- stimulates production of DHEA, DHEA-S and other steroids in adrenal cortex
- suppresses the maturation of follicles in the mother's ovary (instead of LH)

Number of Weeks After Conception	Averge hCG Level (mIU/mL)
First Week	5-50 mIU
1-2 Weeks	50-500 mIU
2-3 Weeks	100-5,000 mIU
3-4 Weeks	500-10,000 mIU
4-5 Weeks	1,000-50,000 mIU
5-6 Weeks	10,000-100,000 mIU
6-8 Weeks	15,000-200,000 mIU
8-12 Weeks	10,000-100,000 mIU



Hormonal regulation of pregnancy: Human placental lactogen (HPL), corticotropin (CRH)

HPL

- human chorionicsomato(mammo) tropin
- produced by the placenta
- increasing concentrations during pregnancy
- stimulates mammary gland growth and milk production, increases the concentration of glucose in the mother's blood
- **affects the growth and development of the fetus**

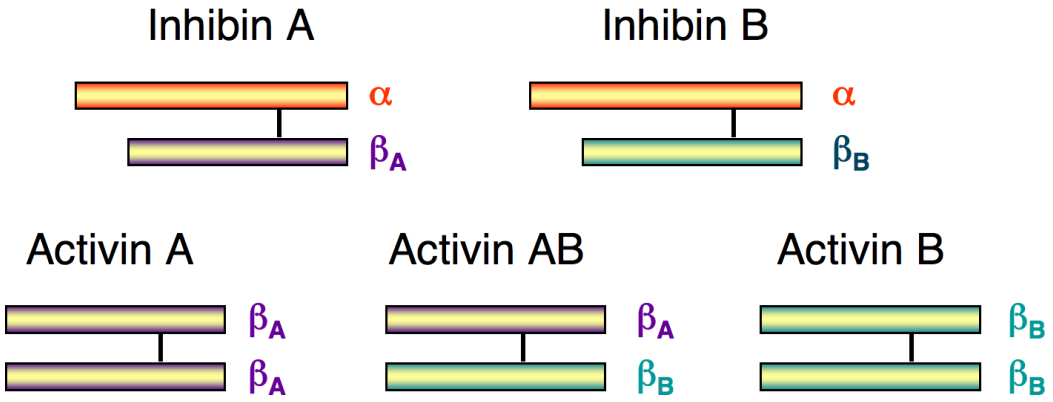
CRH

- produced in the placenta
- the key role in inducing childbirth (the length of pregnancy depends on the rate of its cummulation)
- supports ACTH secretion by fetal pituitary > ↑ cortisol in fetal adrenal glands > ↑ CRH (positive feedback)
- **stimulates DHEA production by fetal adrenal glands > E in the placenta**

- **at the end of pregnancy E predominates over P** > induced expression of **oxytocin receptors** in uterine muscle cells and increasing uterine irritability > oxytocin secretion due to irritation of baroreceptors in the uterus

Activin and inhibin

- belongs to TGF-β protein family (also e.g. anti-Müllerian hormone)
- activin is dimer of identical or very similar β subunits linked by disulfide bridge
- inhibin has the identical β subunit but remotely related α subunit
- gonads, pituitary gland, placenta and other organs (e.g. corpus luteum)
- binding to transmembrane receptors with kinase activity
- almost opposite biological activity



- A supports x I suppresses FSH production and secretion
- they also affect cell proliferation and differentiation, metabolism, immunity or wound healing processes