Sexual hormones

2019

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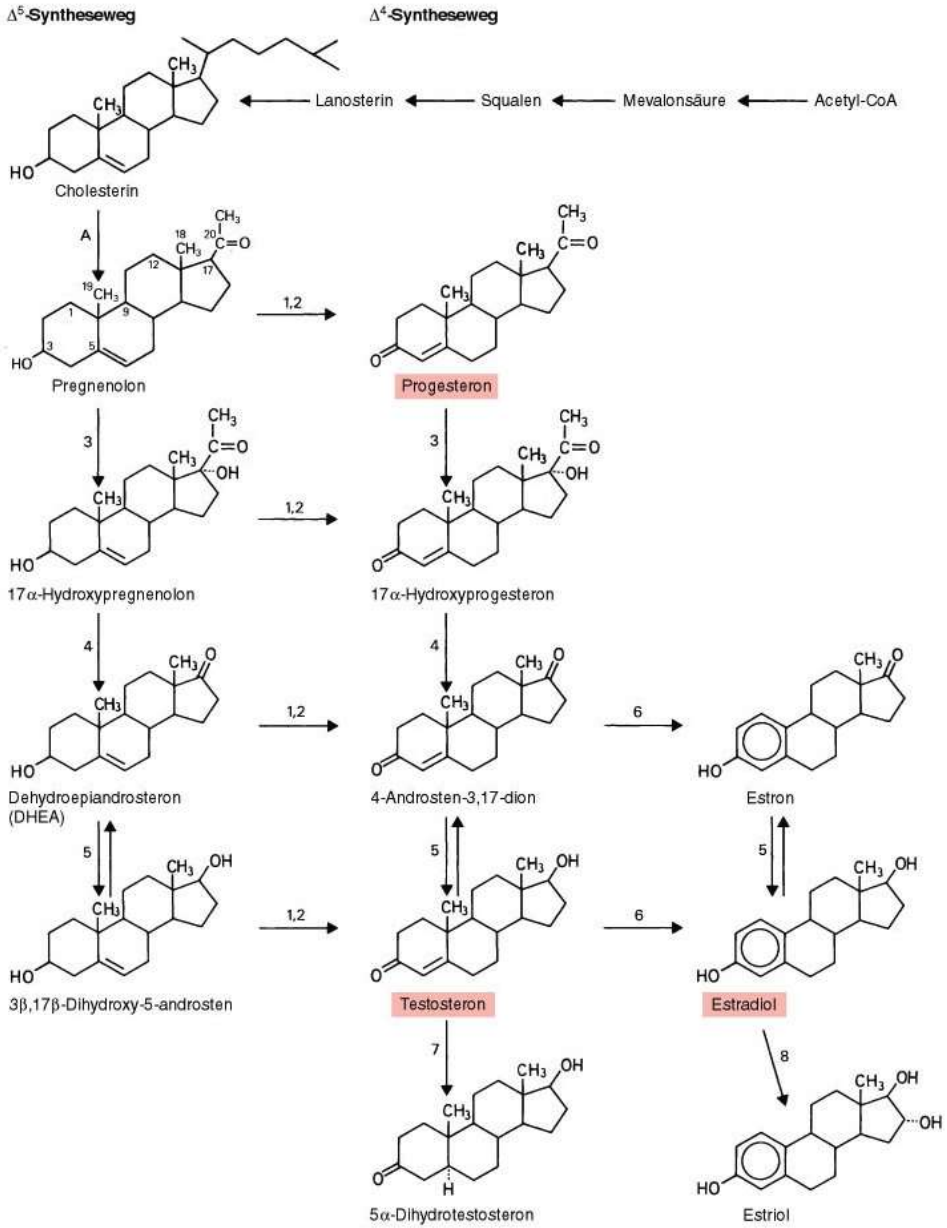
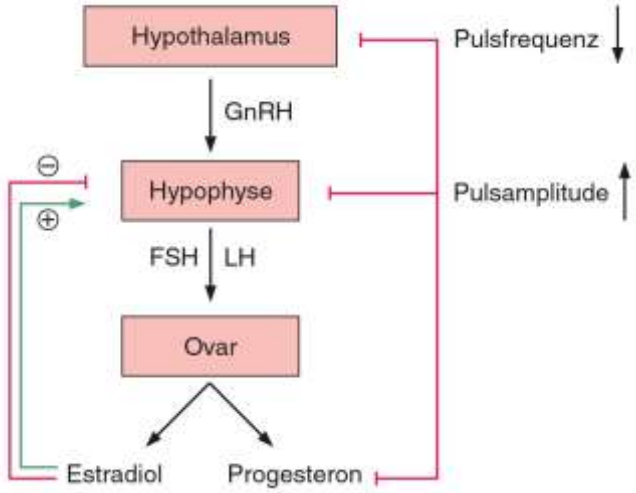
Synthesis of gonadal hormones



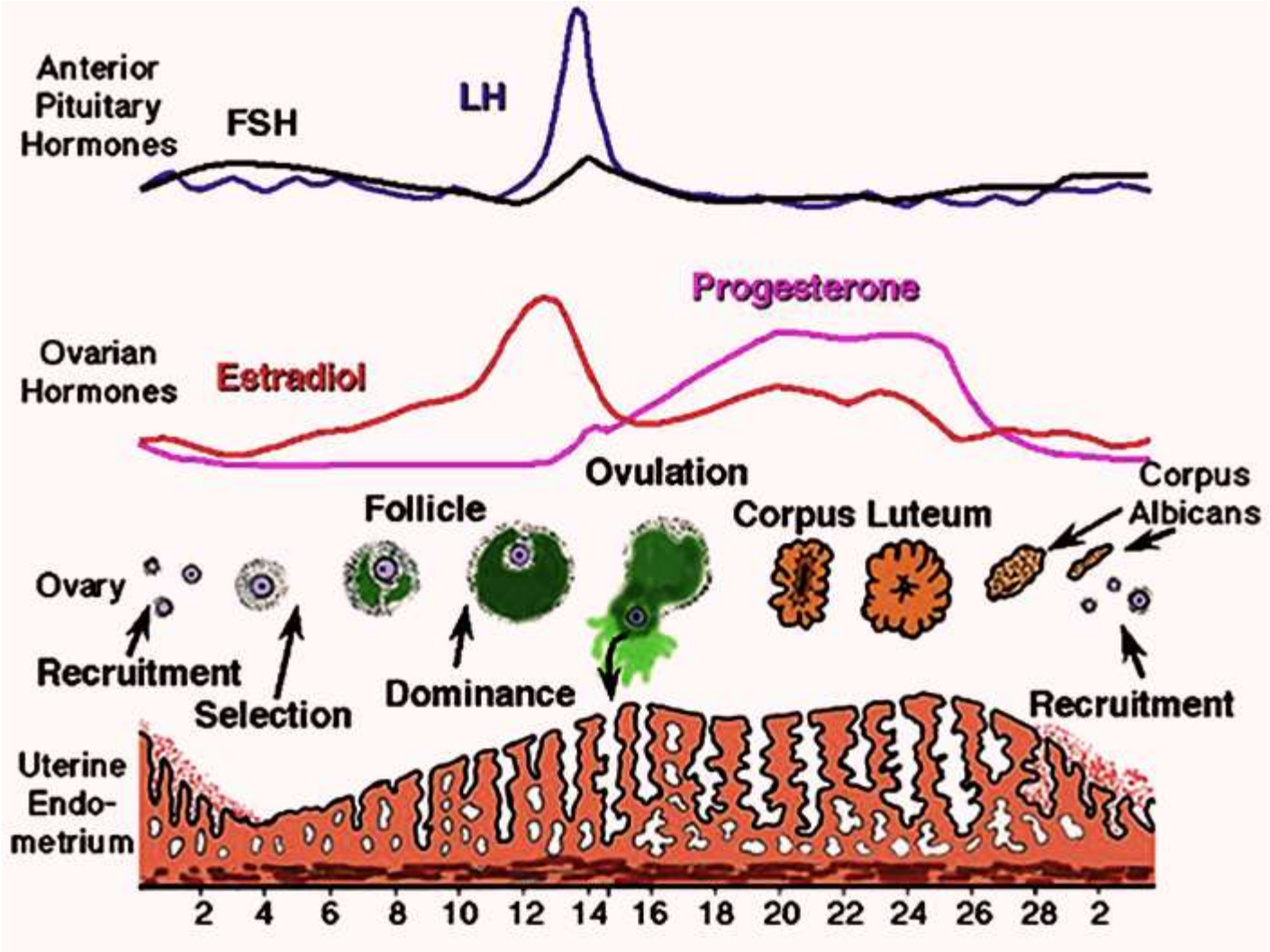
Female sexual hormones

The ovary

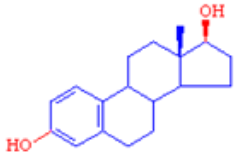
- gametogenic and endocrine functions
  - quescient before puberty
  - at puberty – begins a 30-40 year period of cyclic function (menstrual cycle)
  - menopause
- function controlled by GnRH (hypothalamus) – FSH, LH (pituitary)
- ovarian hormones: estrogens, progestins, others



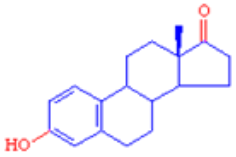
The menstrual cycle

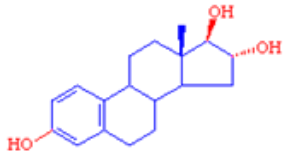


The estrogens

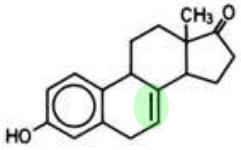


- **Natural estrogens**
  - **estradiol – the major secretory product of the ovary**

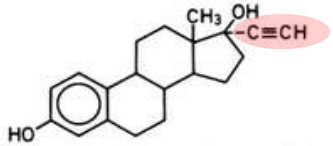




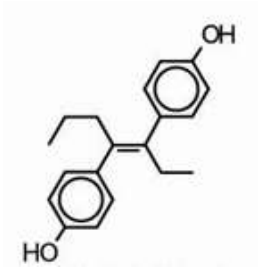
  - **estrone and estriol formed in the liver from estradiol, or in the peripheral tissues from androgens (androstenedione)**
  - **equine estrogens**
  - **phytoestrogens**



- **Synthetic estrogens**
  - **steroidal structures**
    - **ethinylestradiol,** mestranol, quinestrol



  - **nonsteroidal compounds**
    - dienestrol, diethylstilbestrol, chlorotrianisene, methallenestril, benzestrol, hexestrol, methestrol



Pharmacokinetics of estrogens

Natural estrogens

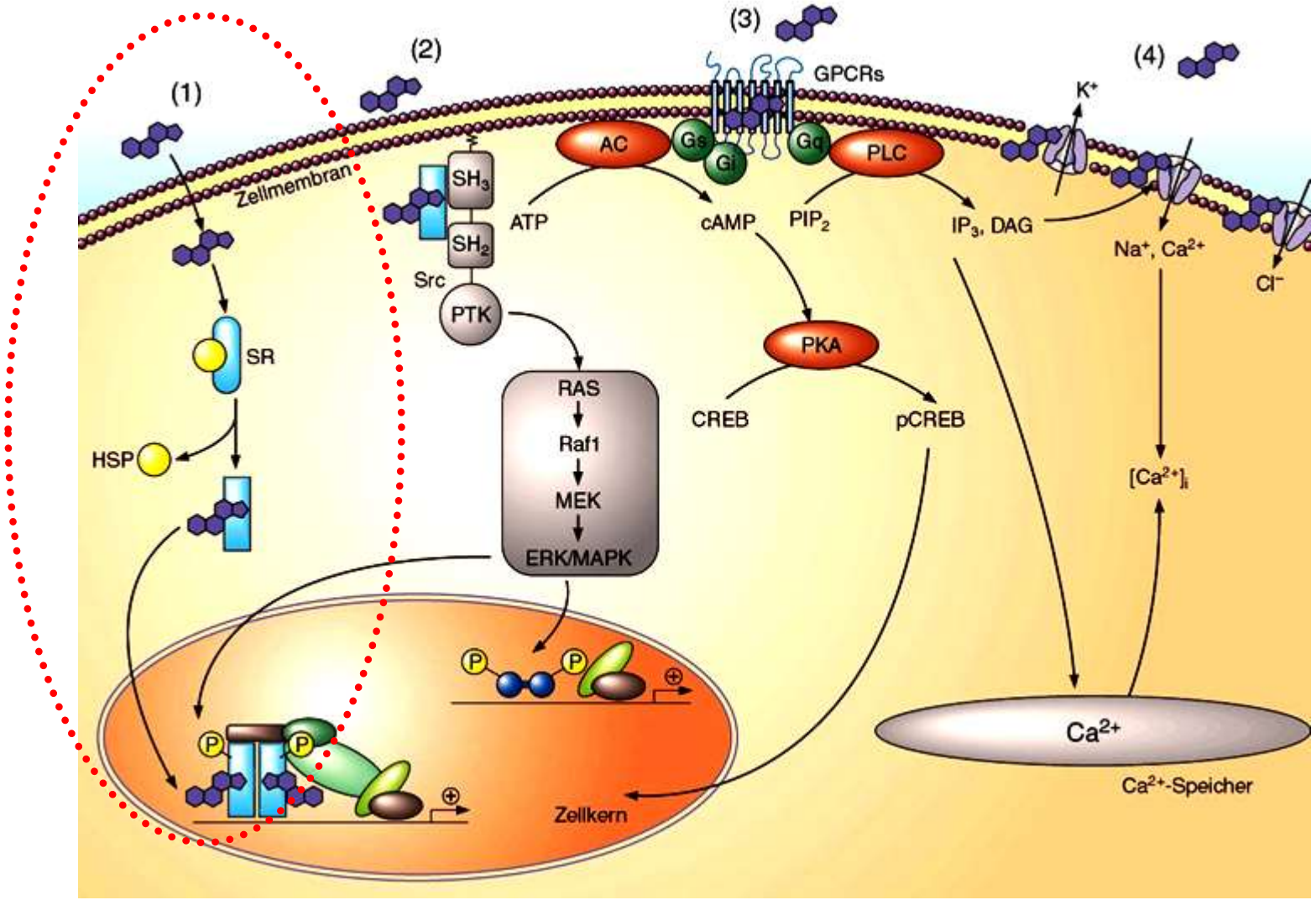
- high first pass metabolism
  - high ratio of hepatic to peripheral effects
    - increases the incidence of some side effects
      - undesired: coagulation, biliary
      - advantageous: lipid profile
    - to avoid: transdermally, as an injection, or locally (vaginal use)
  - conjugated estrogens (e.g. estradiol valerate)
    - i.m. depot
- estradiol binds to SHBG (and to albumin) in the circulation
- excretion in part with bile – enterohepatic cycling

Synthetic estrogens

- good oral bioavailability

Mechanism of estrogen action

- **intracellular receptor – gene activation**



Pharmacological effects of estrogens

- **estrogens promote proliferation (endometrium, breast)**
- **cooperation with progestins**
- **female sexual maturation and growth, secondary sex characteristics, female libido**
- **endometrial effects – development of endometrial lining**
- **metabolic and cardiovascular effects**
    - **normal structure and function of the skin and blood vessels**
    - **decrease the rate of resorption of bone**
    - **higher levels of CBG, TBG, SHBG, transferrin, fibrinogen**
    - **mild, advantageous changes in lipoprotein, triglyceride and cholesterol levels**
- **blood coagulation is enhanced (increased synthesis of coagulation factors)**
- **activation of the stress and the sympathetic systems**
- **sodium retention, edema**

Clinical uses of estrogens

- hormone replacement
  - primary hypogonadism
    - replacement therapy, started at 11-13 years of age
  - postmenopausal hormonal therapy
    - either estrogen monotherapy
    - or in combination with progestins (if the patient has intact uterus)
- estrogens + progestins: ovarial suppression
  - hormonal contraception
  - other reasons
    - severe menstrual problems: intractable dysmenorrhea, polymenorrhea, dysfunctional bleeding, premenstrual syndrome
    - treatment of hirsutism and amenorrhea due to excessive secretion of androgens by the ovary

Adverse effects of estrogens

- increased risk of endometrial carcinoma
  - progestins are protective
- increased risk of breast cancer
  - progestins are not protective
- increased blood coagulation
  - increased risk of stroke and venous thrombosis
- postmenopausal uterine bleeding
- nausea, breast tenderness, hyperpigmentation
- increase in frequency of migraine headaches, cholestasis, gallbladder disease, hepatic adenomas
- diethylstilbestrol
  - increases the risk of the vaginal adenocarcinoma in women whose mother was treated during pregnancy – should be avoided during pregnancy

Contraindications of the estrogens

- **patients with estrogen-dependent neoplasms (endometrial, breast cancer)**
- **ensometriosis**
- **patients with undiagnosed genital bleeding**
- **severe liver disease**
- **history of thromboembolic disorder**
- **heavy smokers**

SERM – selective estrogen receptor modulators

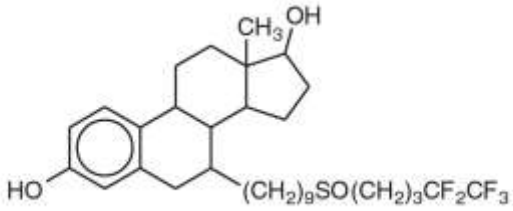
	Estradiol	Clomifen	Tamoxifen	Toremifen	Raloxifen
endometrium	+++	-	+	?	Ø
breast	+++	-	---	---	---
bones	+++	-	+	Ø	++
vasomotor effects	+++	-	+(+)	+(+)	+(+)
advantageous effects on lipid levels	+++	-	+	++	+

SERM - indications

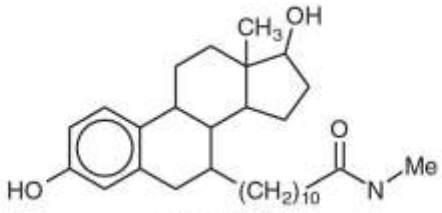
- **Clomifen**
  - **ovulation-inducing agent**
- **Tamoxifen, toremifene**
  - **used in palliative treatment of breast cancer in postmenopausal women**
- **Raloxifene, bazedoxifene**
  - **prevention of postmenopausal osteoporosis**

Antiestrogens I.

- **Estrogen receptor antagonists**
  - **Fulvestrant**
    - **indication: breast cancer resistant to tamoxifen in postmenopausal women**
    - **only i.m.**



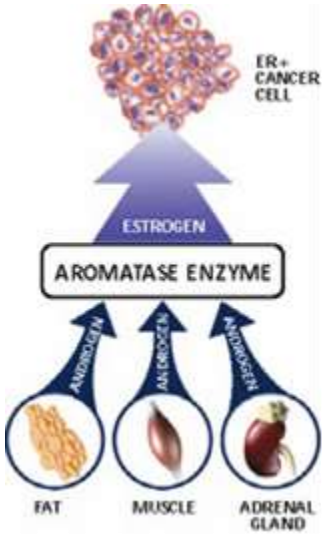
Fulvestrant (ICI 182,780)

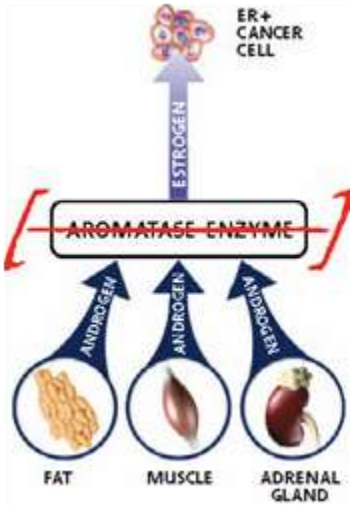


ICI 164,384

Antiestrogens II.

- **Aromatase inhibitors**
  - **steroid inhibitors: exemestane, formestane**
  - **nonsteroidal inhibitors: anastrozole, letrozole, fadrozole**
    - **indication: breast cancer resistant to tamoxifen**





- **GnRH analogs, antagonists**

The progestins

- natural progestin: progesterone, produced by corpus luteum
- orally ineffective (first pass metabolism) – i.m. administration
- physiologic effects (intracell. receptors – gene expression)
  - main action: inhibit proliferation, promote differentiation (exc. breast - involvement in proliferation as well) - cooperation with estrogens
    - endometrium – maturation and secretory changes following ovulation
    - breast – proliferation, then alveolobular development of the secretory apparatus
    - implantation, maintenance of pregnancy, inhibition of ovulation
    - increase of body temperature
    - metabolic effects – fat deposition, effects on carbohydrate metabolism, ketogenesis
    - competition with aldosterone receptor (decreased Na reabsorption)
    - respiratory effect – ventilatory response to CO_2 is increased
    - depressant and sedative/hypnotic effects on the brain
    - increased urinary N excretion (catabolic effect)

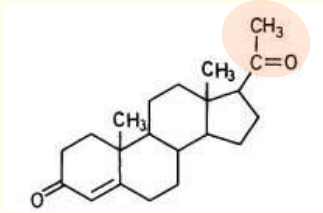
Synthetic progestins

- better oral bioavailability (exc. hydroxyprogesterone)

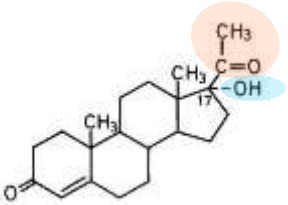
- **Pregnans** (21-carbon compounds)
  - hydroxyprogesterone-capronate, medroxyprogesterone-acetate, megestrol-acetate, drospirenone, cyproterone-acetate
  - closely related to progesterone

- Estrans (**19-norsteroids**)
  - e.g. norethisterone, norethynodrel, ethynodiol, lynestrenol
  - do not support pregnancy, produce non-physiologic changes of the endometrium, inhibit implantation, more effective gonadotropin inhibitors
  - androgen/anabolic action

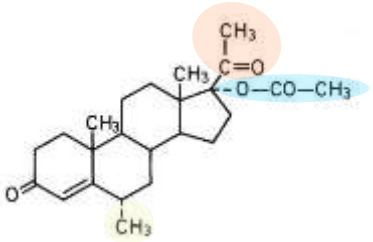
- **Gonans** (13-ethyl derivatives of 19-norsteroids)
  - norgestrel, levonorgestrel, desogestrel, norgestimate, norelgestromin, gestodene, etonorgestrel



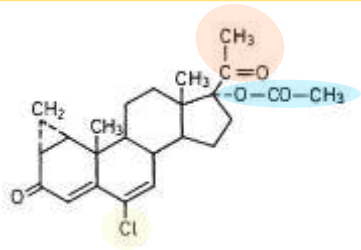
progesterone



17-hydroxyprogesterone

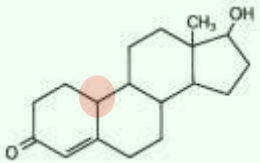


medroxyprogesteron-acetate

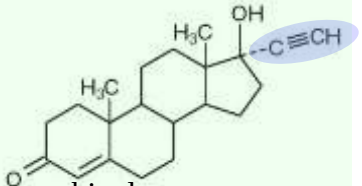


cyproterone-acetate

pregnans

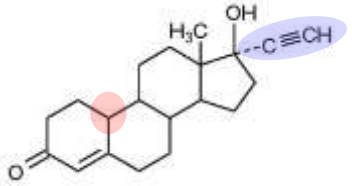


19-nortestosterone

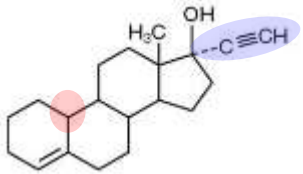


ethinyltestosterone
(ethisterone)

androgenic precursos

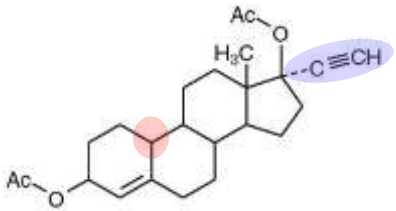


norethisterone



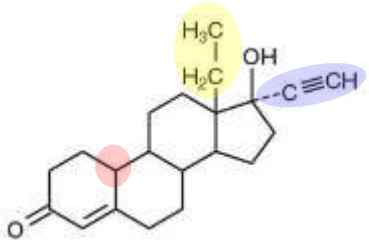
lynestrenol

19-norsteroids

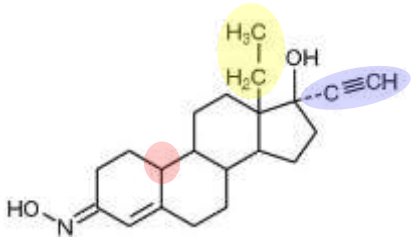


etynodiol-diacetate

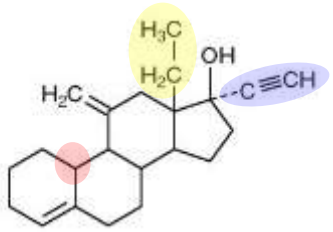
gonans



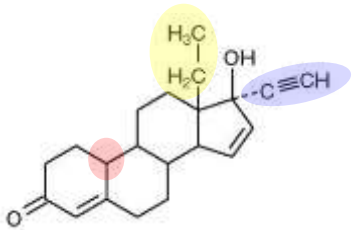
norgestrel



norgestimate



desogestrel



gestodene

	Effects					
	Estrogen	Anti-estrogen	Androgen	Anti-androgen	Gluco-corticoide	Anti-mineralo-corticoide
Progesteron	Ø	+	Ø	(+)	(+)	+
Megestrol-acetate	Ø	+	Ø	Ø	+	
Medroxyprogesteron-acetate	Ø	+	(+)	Ø	+	
Chlormadinon-acetate	Ø	+	Ø	+	+	Ø
Cyproteron-acetate	Ø	+	Ø	+	+	Ø
Drospirenone	Ø	+	Ø	+	Ø	+
Dienogest	Ø	+	Ø	+		
Norethisterone	(+)	+	+	Ø	Ø	Ø
Lynestrenol	+	+	+	Ø	Ø	Ø
Etynodiol-diacetate	(+)	+	+	Ø	Ø	Ø
Norethynodrel	+	-	(+)	Ø	Ø	Ø
Norgestrel	Ø	+	(+)	Ø	Ø	Ø
Norgestimat	Ø	+	(+)	Ø		
Desogestrel	Ø	+	(+)	Ø		Ø
Gestodene	Ø	+	(+)	Ø	(+)	Ø

Clinical uses of progestins

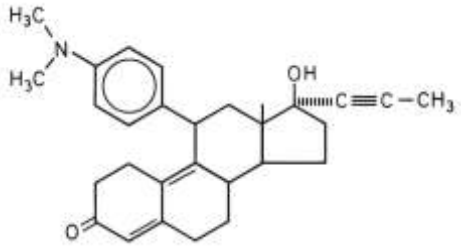
- primary hypogonadism - hormone replacement therapy (combination with estrogens)
- postmenopausal hormone therapy (to reduce the risk of endometrial cancer caused by estrogens)
- hormonal contraception
- long-term ovarian suppression
    - treatment of dysmenorrhea, endometriosis, bleeding disorders when estrogens are contraindicated
- prevention of preterm birth ?
- palliative treatment of estrogen-dependent tumors
- medroxyprogesterone – prevent menstruation but does not arrest bone maturation in children with precocious puberty

Adverse effects of gestagens

- increased risk of breast cancer
- decreased HDL
- impairment of glucose tolerance
- elevation of blood pressure
- headache, psychic disturbances
- androgenic/anabolic adverse effects of 19-norsteroids

Progesterone antagonists

- **Mifepristone (RU 486)**
  - **19-norsteroid, progesterone receptor antagonist (SPRM?)**
  - **terminates early pregnancy (in combination with vaginal PGE_1 or with its analogue misoprostol p.o.)**
  - **adverse effects of the combination: vomiting, diarrhea, abdominal pain, vaginal bleeding**
  - **antiglucocorticoid activity**
  - **potential indications: endometriosis, breast cancer, meningeoma**



- **ulipristal – morning after pill, treatment of myomas**

Hormonal contraception

- oral contraceptives
- parenteral (depot) contraceptives
- trasdermal contraceptives
- contraceptive implantates
- local contraceptives
- postcoital contraceptives

Postmenopausal hormonal therapy

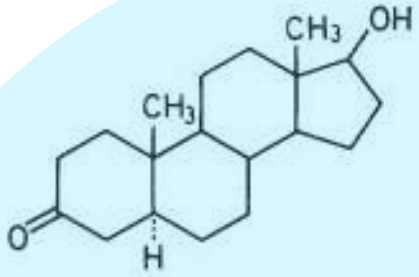
- **Therapeutic goal**
  - **symtomatic relief of atrophic vaginitis and other local problems by local use of estrogens**
  - **symptomatic relief of hot flushes, sweathing, insomnia, climacteric psychopathologic states (mental depression) with a short-term hormonal therapy**
  - **long-term prevention and treatment of osteoporosis**
- **usually the treatment is very effective**
- **estrogens alone relieve the symptoms, but in case of systemic use and intact uterus progestins are added to reduce the risk of endometrial cancer**
- **adverse effects**
  - **local and short-term systemic treatment is less problematic**
  - **chronic systemic postmenopausal hormone replacement increases the risk of the cardiovascular complications and breast cancer**

Male sexual hormones

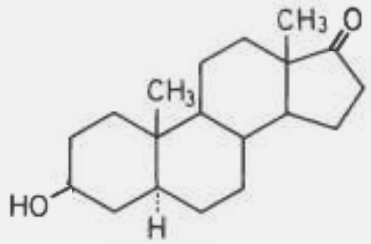
The testis

- gametogenic functions (controlled by FSH)
- endocrine functions
  - the main androgen secreted by testis is testosterone (Leydig cells – stimulated by LH)
  - smaller amounts of dihydrotestosterone (potent), androstenedione and dehydroepiandrosterone (weak androgens) are also secreted

Testosterone

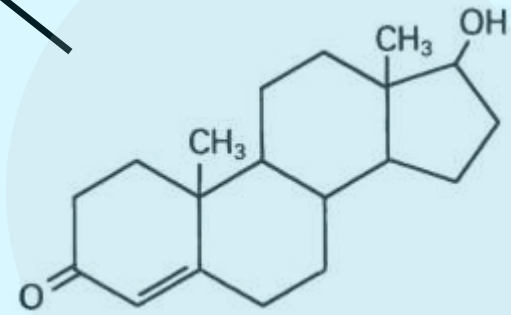


DHT



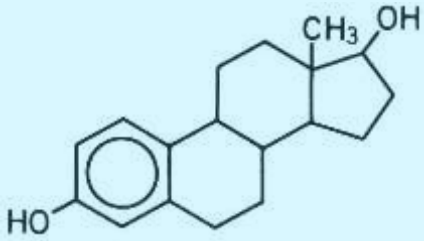
Androsterone

aktive metabolites

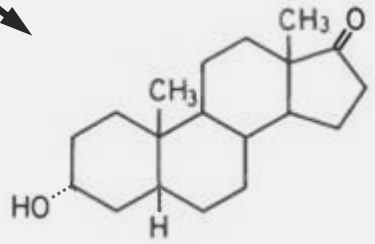


Testosteron

inactive metabolites



Estradiol



Etiocholanolone

Testosterone

- **intracellular receptor – gene activation**
- **good absorption, but low oral bioavailability (first pass metabolism) - injection or transdermal use**
  - **testosterone-undecanoate – also oral**
- **pharmacological actions – androgenic and anabolic effects**
  - **in young men – development of secondary sex characteristics**
  - **in adult women – facial and body hair, deepening of voice, enlargement of clitoris, frontal baldness etc.**
  - **in adult men – maintenance of libido, spermatogenesis**
  - **anabolic effects – reduced nitrogen excretion, increased protein synthesis, decreased protein breakdown (more pronounced in women and children)**

Steroids with androgenic/anabolic actions

• Testosterone	1:1
• Methyltestosterone	1:1
• Fluoxymesterone	1:2
• Methandienone	1:3
• Oxymetholone	1:3
• Ethylestrenol	1:4 - 1:8
• Oxandrolone	1:3 - 1:13
• Nandrolone	1:3 - 1:6
• Stanozolol	1:3 - 1:6
• Dromostanolone	1:3 - 1:4

Ben Johnson
1988, Seoul

Clinical uses of androgens and related steroids

- **androgen replacement – hypogonadism in men, after castration (testosterone, testosterone undecanoate, mesterolone)**
- **protein anabolic agents after trauma, surgery, prolonged immobilization**
- **other indications**
  - **danazol (weak androgen) – endometriosis**
  - **danazol, stanozolol - hereditary angioedema (long-term therapy – increased synthesis of C1-esterase-inhibitor in the liver)**
- **illegal use – sport**

Adverse effects of androgens and related steroids

- masculinizing action in women and children (hirsutism, acne, deepening of the voice etc.)
- some androgens with progestational activity – increased cardiovascular risk, endometrial bleeding upon discontinuation in women
- sodium retention, edema
- C-17-alkyl-substituted steroids (most anabolic agents) – hepatic dysfunction (AST, bilirubin, cholestasis, hepatic tumors)
- older males – prostate hyperplasia
- contraindication: pregnancy, prostate cancer, infants and young children, breast cancer in male

Antiandrogens

- androgenic suppression with GnRH-analogs
- steroid synthesis inhibitors
  - ketoconazole
    - antifungal drug, inhibitor of adrenal and gonadal steroid synthesis
    - clinical trials in hirsutism (women) and prostate cancer – not encouraging
    - causes sexual disturbances during the antifungal treatment
  - 17-hydroxylase inhibitors
    - abiraterone – treatment of prostate cancer
- 5α-reductase inhibitors
  - finasteride, dutasteride (longer acting)
    - moderately effective in reducing prostate size in men with benign prostate hyperplasia
    - may be useful in male baldness and female hirsutism

Antiandrogens

- **Androgen receptor antagonists**
  - **bicalutamide, enzalutamide, flutamide, nilutamide**
    - **strong and pure androgen antagonists**
    - **used in the treatment of metastatic prostate cancer**
    - **flutamide has a mild hepatotoxicity**
  - **cyproterone acetate**
    - **strong progestational activity**
    - **treatment of hirsutism in women, decreases excessive sexual drive in men, useful in prostate cancer, and used in alopecia in women (combination therapy with ethinylestradiol)**
  - **spironolactone**
    - **diuretic agent, aldosterone and androgen antagonist, inhibits testosterone synthesis, used in the treatment of hirsutism in women**

GnRH

- **decapeptide, produced by the arcuate nucleus of the hypothalamus**
- **controls the release of the gonadotropins FSH and LH**
- **GnRH analogs have a longer half-life (3 hours compared with GnRH – 4 minutes), they can be given intranasally**
    - **leuprorelin, nafarelin, goserelin, histerelin, buserelin, triptorelin**
- **diagnostic use: delayed puberty**

(constitutional delay – normal LH response
hypogonadotropic hypogonadism due to pituitary/hypothalamic disease – impaired LH response)

GnRH

- **therapeutic uses**
  - **stimulation – pulsatile GnRH (gonadorelin) therapy: every 90 minutes – infertility caused by hypothalamic hypogonadotropic hypogonadism in both sexes**
  - **suppression – continuous therapy (GnRH analogs) – prostate cancer, uterine fibroids, endometriosis, polycystic ovary syndrome, precocious puberty**
  - **in vitro fertilization programs – suppression followed by exogenous gonadotropins – synchronous follicular development**
- **GnRH antagonists**
  - **ganirelix, abarelix, degarelix, cetrorelix**
  - **treatment of prostate cancer, in vitro fertilization programs**

FSH

- glycoprotein hormone produced in the anterior pituitary
- stimulates gametogenesis and follicular development in women and spermatogenesis in men
  - follitropin beta – modified FSH for therapeutic use
  - urofollitropin – human FSH extracted from the urine of postmenopausal women without LH
  - hMG (menotropins) – FSH-LH combination
- indication: pituitary or hypothalamic hypogonadism with infertility, in vitro fertilization programs

LH

- glycoprotein hormone produced in the anterior pituitary
- primarily responsible for regulation of gonadal steroid hormone secretion
  - human chorionic gonadotropin (hCG: LH in pregnancy) – LH substitute
- diagnostic use
  - prepubertal boys with undescended gonads – distinguish truly retained (cryptorchid) testis from retracted (pseudocryptorchid)
- therapeutic uses
  - induce ovulation (in combination with human menotropins)
  - stimulate testosterone secretion (hypogonadotropic hypogonadism)
  - AIDS-related Kaposi's sarcoma – injection into the lesions cause regression