

Gonadal Hormones & Inhibitors

Estrogens

Natural estrogens

estradiol

estrone

estriol

Steroidal synthetic

Ethinyl estradiol

Mestranol

Quinestrol

Nonsteroidal synthetic

Diethylstilbestrol

Chlorotrianisene


Methallenestril

Prolonged use (alone) in
pharmacological quantities :::::

endometrial hyperplasia

Q. what if estrogens and their active metabolites are excreted in bile and reabsorbed?

Q. this applies to which which route?

 clotting factors
renin substrate
TBG, SHBG, CBG

Q. think of an alternative route

Q. is this a problem for
physiological release?

Clinical Uses

Oral Contraceptives

Clinical Uses

Primary hypogonadism

failure in ovarian development

11-13 years of age

estrogen / progestin (added later)

stay tuned...

Clinical Uses

Primary hypogonadism

Continuous low-dose (about 1 year)
Followed by cyclic administration
of higher doses

Clinical Uses

Acne

Age ≥ 15

Estrogen+progesteron

At least 6 months for those
who do not respond to topical agents

Clinical Uses

Postmenopausal

Hormone

Replacement

Osteoporosis

Clinical Uses

Postmenopausal

Hormone Replacement

- Sleep
- Vasomotor
- Genital atrophy
- Cancer

W
no
neut

Routine hormonal therapy
is questionable

cial effects on CV risk!!

Risk: Breast cancer !!

Q. Which route
may be
associated
with less
cardiovascular
risk?

- Early menopause requires HRT
- Estrogen only is OK for hysterectomized women
- Osteoporosis is higher in thin smokers 😊
- Treatment MUST be personalized
- add progestin to reduce endometrial issues, but...

Unwanted

Nausea

Edema

Headaches

Hypertension

Breast tenderness

Cyclical bleeding (!)

STOP smoking

Migraine (caution)

Hypertension (caution)

< 6 months postpartum
(caution)

- pregnancy
- undiagnosed abnormal vaginal bleeding
- active thromboembolic disorder or acute-phase MI
- suspected or active breast or endometrial cancer
- active liver disease with abnormal liver function tests
- porphyria cutanea tarda

Selective Estrogen Receptor Modulators

Tamoxifen & Related Drugs

Tamoxifen

- Nonsteroid, given orally
- Estrogen-agonist effect reduces osteoporosis, has beneficial effects on lipids

Risk: Endometrium cancer

Palliative treatment of advanced breast cancer in postmenopausal women

Raloxifene

Does not stimulate endometrium or breast

Indication: Postmenopausal osteoporosis, prophylaxis of breast cancer

PROGESTINS

Natural Progestins: Progesterone

Precursor to **estrogens,**
androgens, and **adrenal**
steroids

Synthesized in the ovary, testis, and
adrenal from **cholesterol**

Large amounts synthesized by the
placenta

Pharmacokinetics

Rapidly absorbed by any route

$t_{1/2}$ 5 min

High dose micronized progesterone preps developed for progestational effect

Physiological Effects

- Competes with aldosterone for the receptor: Increased aldosterone secretion during pregnancy
- Increases body temperature
- Depressant and hypnotic

in CNS

Physiological Effects

- Development of secretory apparatus in the breast
- Maturation and secretory changes in endometrium

Synthetic Progestins

Progesterone

Hydroxyprogesterone caproate

Medroxyprogesterone acetate

Megestrol acetate

antagonize
aldosterone
receptor

Desogestrel

Norgestimate

Gestodene

no androgenic
activity

Clinical Use

1. Postmenopausal HRT
2. Hormonal contraception
3. Previously used for threatened or habitual abortus

Adverse Effects

May increase blood pressure

The more androgenic reduce

HDL levels in women

Antagonists

Mifepriston

- Progesteron and glucocorticoid receptor antagonist
- Luteolytic
- 600mg single dose, postcoital contraceptive
- Major indication, terminate early pregnancy:
 - 400mg/ 4 days
 - 800mg/ 2 days

NOT AVAILABLE in Turkey

Antagonists

Danazol

- Weak progestational, androgenic, and glucocorticoid activities
- Suppresses ovarian function
- Major indication, endometriosis:

600mg/day,

reduced to 400mg in one month

200mg in two months

Marked improvement in 3-12 months

- Side effects: weight gain, edema, acne, oily skin, increased hair growth, deepening in voice, hot flushes, muscle

BIRTH CONTROL

Hormonal Contraception

Mechanism of Action

- 1. Selective inhibition of pituitary function**
- 2. Combination agents also change cervical mucus, uterine endometrium, motility and secretion in the uterine tubes**
- 3. Chronically, depression of ovary:**
 - 75% ovulate in the first cycle**
 - 97% ovulate in the third cycle**
 - 2% remain amenorrheic for years**

Combination Drugs

Estrogen + Progesteron
Mono-, bi-, triphasic

**Ethinyl estradiol +
(0.01mg- 0.04mg)**

**Norethindrone
acetate**

Desogestrel

Norethindrone

Norgestrel

Ehtynodiol

diacetate

...

(0.05mg-0.75)mg

Contraception with Progestins Alone

- Oral or implantation
- Norethindrone or norgestrel
- 150 mg depot medroxyprogesterone acetate (DMPA) every 3 months:
unpredictable spotting, amenorrhea common
- Ovulation suppression up to 18 months after cessation
- sc implanted capsules effective for 5-6 years with low hormone levels

Useful in patients with hepatic disease, hypertension, thromboembolism

Side effects: headache, dizziness, bloating, weight gain, reduction of glucose tolerance

Postcoital Contraception (*Morning after contraception*)

Postcoital Contraception (*Morning after contraception*)

Estrogen alone or combination with progestins

conjugated estrogens:

10mg, 3x daily, 5 days

ethinyl estradiol:

2.5mg, 2x daily, 5 days

diethylstilbestrol:

50mg/day, 5 days

L-Norgestrel:

0.75mg, 2x, 1 day

norgestrel 0.5mg + ethinyl estradiol 0.05mg

2 tablets immediately,

2 tablets at 12 hours

Etkin madde	Kullanım şekli
Ulipristal, 30 mg (Ella®)	İlk 120 saat (5 gün) içinde1 tablet
Östrojen, 10 mg	Günde 3 kez
Etinilöstradiol, 2.5 mg	Günde 2 kez, 5 gün
Dietilstilbestrol, 50 mg	Günde 1 kez, 5 gün
Levonorjestrel, 1.5 mg (Norlevo®)	Bir kez (72 saat içinde)
Norjestrel, 0.5 mg + Etinilöstradiol, 0.05 mg	2 tablet + 2 tablet (ilk dozdan 12 saat sonra)

Postcoital Contraception *(Morning after contraception)*

**When treatment is begun
within 72 hours, 99% effective**

Nausea and vomiting 40%

Anastrozol (Arimidex[®]), Letrozol (Letroks[®]),
Eksemestan (Aromasin[®])

- Aromatase (responsible for estrogen synthesis) inhibitors
- In patients resistant to tamoxifen

Fulvestrant (Faslodex[®]) and ICI 164384

<http://www.faslodex.com/fulvestrant/downloader.aspx>

- Reduce estrogen receptor number
- No agonist effect on estrogen receptor
- Advanced breast cancer
- Once a month application

ANDROGENS

Most important androgen: testosteron
dihydrotestosterone
androstenedione
dehydroepiandrosterone

Methyltestosterone (1:1)
Fluoxymesterone
~~Nandrolone, Oksandrolone~~
Stanozolol
!! Oksimetolon (1:3)

Testosterone
(enanthate, propionate, etc.)

- Intracellular receptors
- primary and secondary sex characteristics in men
- Anabolic action: increase in muscle size and strength and increase red blood cells; reduction in urea nitrogen
- Many androgens synthesized to increase anabolic effects only, however all **so-called anabolic** steroids have **full androgenic effects in human**

In many tissues
(including **testis**
and **hair follicle**),

DHT is the
major active androgen

Clinical Use

Replacement therapy in
hypogonadism

To promote weight gain in patients
with wasting syndromes

In the past, they have been used to
stimulate red blood cell production

Caution!!!

Anabolic effects exploited illicitally
by athletes

Paradoxically, excessive dose in men
can result in feminization due to
conversion to estrogens
(gynecomasty, testicular shrinkage,
infertility)

ANTIANDROGENS

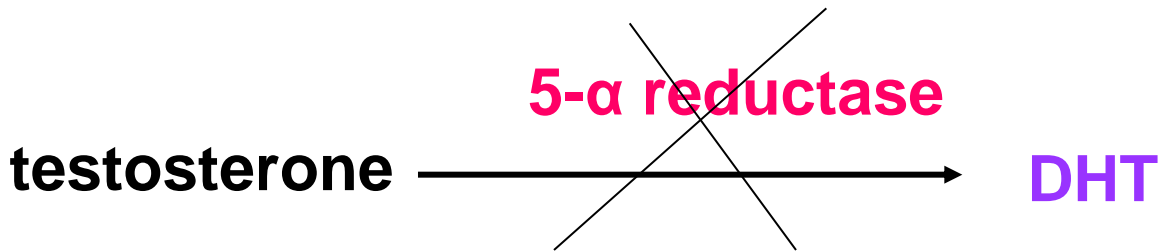
- Benign and malignant prostate cancer

(bicalutamide, nilutamide..)

- Precocious puberty
- Hair loss
- Hirsutism

ANTIANDROGENS

Ketoconazole (antifungal) inhibits steroid synthesis



Finasteride, Dutasteride

Finasteride for benign prostatic hypertrophy and, at a lower dose, to prevent hair loss