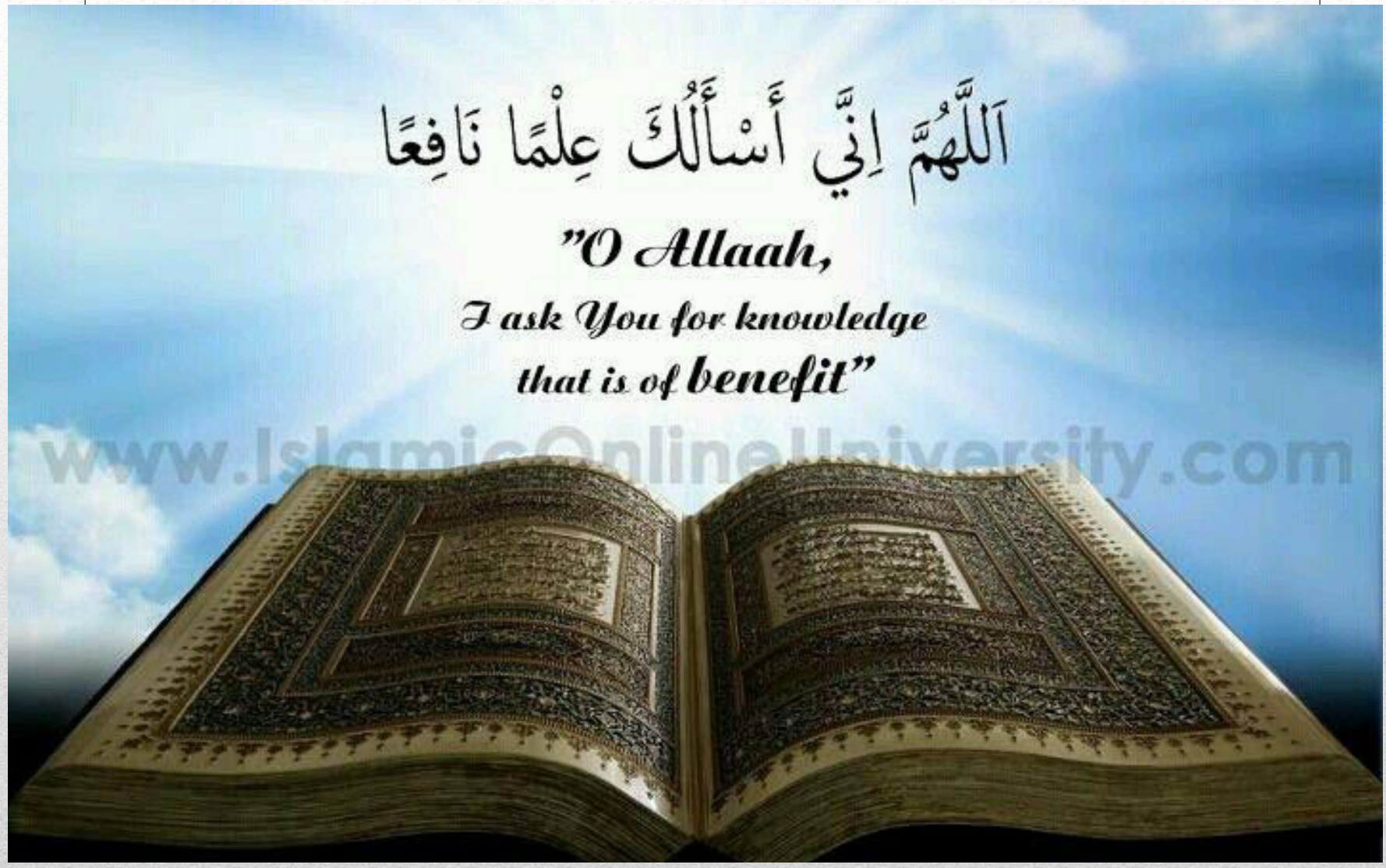
اَللَّهُمَّ اِنِّي أَسْأَلُكَ عِلْمًا نَافِعًا
"O Allaah,
I ask You for knowledge
that is of benefit"
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Ovulation Inducing Agents
Anti Androgens
Male Contraception

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Endocrine & Reproduction-II Module
Theme-5; infertility & pregnancy
4th Year MBBS

Aims And Objectives

By end of this presentation you would be able to

- Describe ovulation inducing agent
- Classify Anti-androgens
- Describe their clinical uses, and adverse effects
- Male Contraception
  - Enlist the drugs used for male contraception
  - Describe the role of gossypol as male contraceptive agent

Clomiphene Citrate

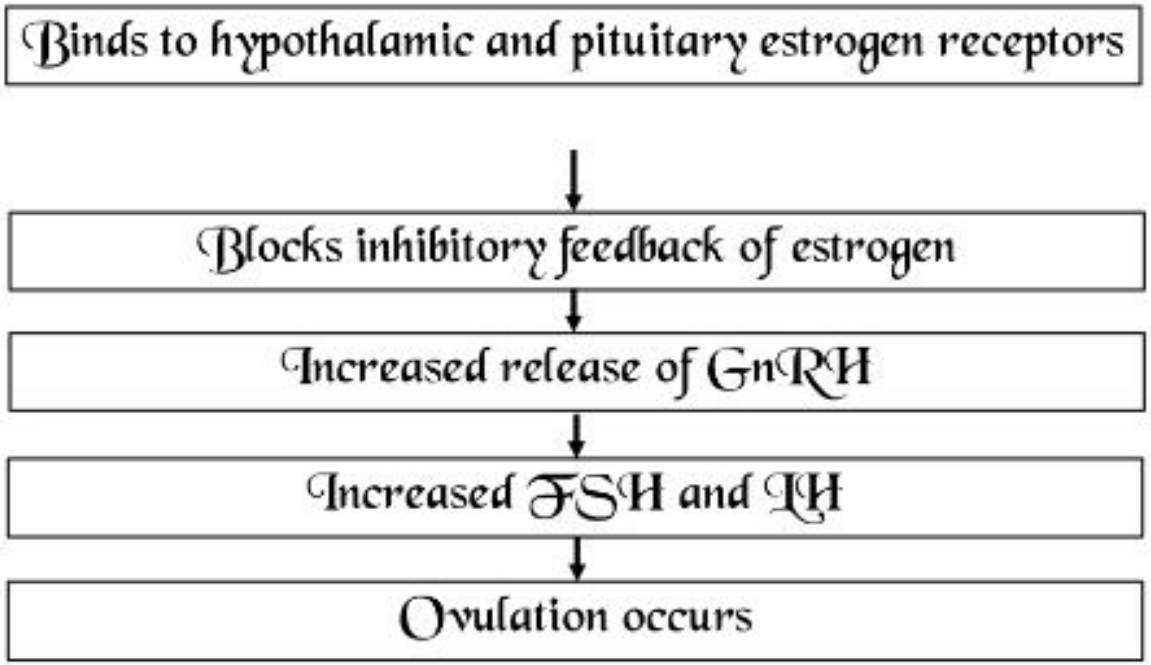
Clomiphene citrate, a partial estrogen agonist

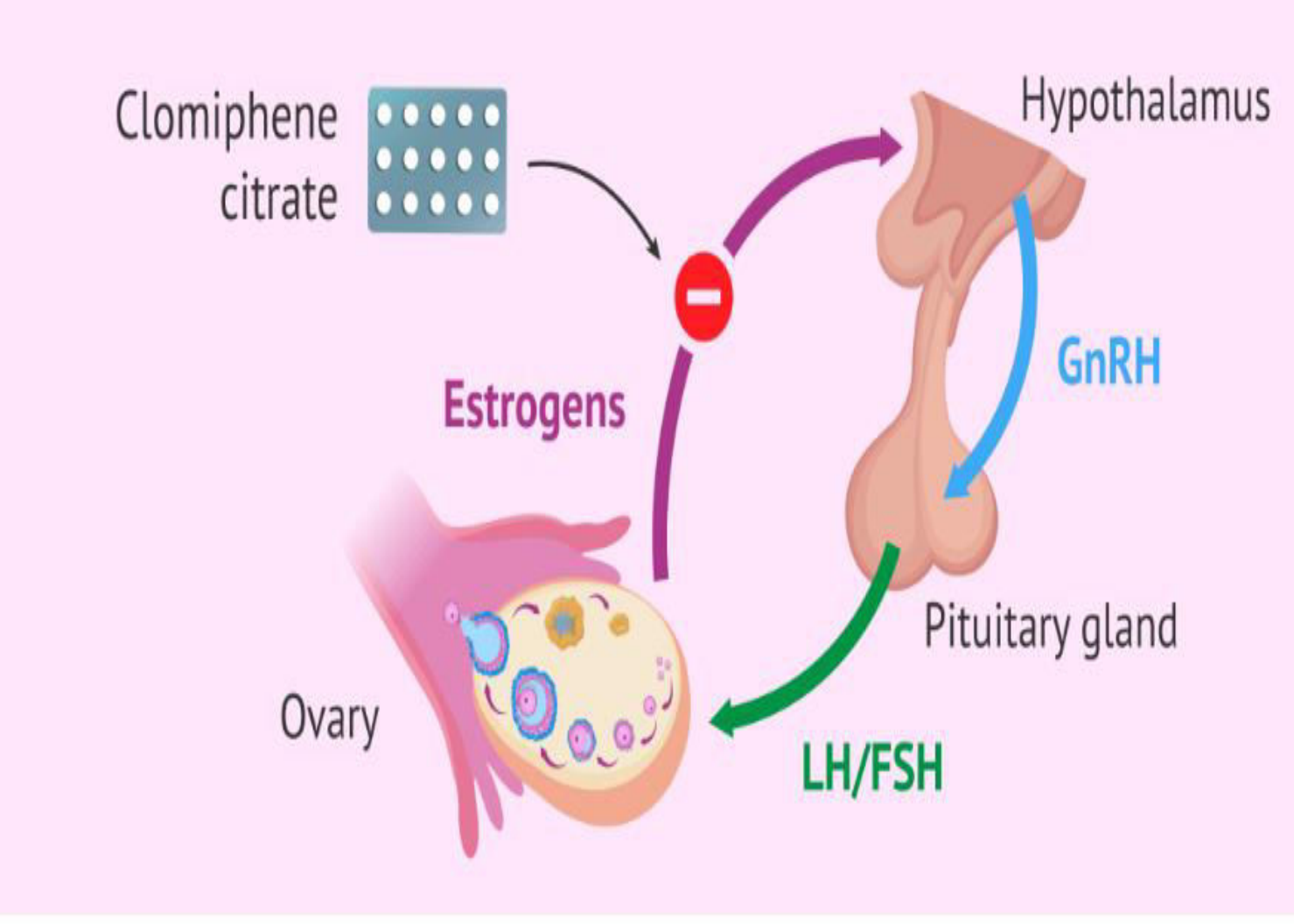
- Nonsteroidal, Synthetic Compound, Triphenylethylene Derivative
- Structural Similarity To Estrogen
- Antiestrogenic Effect
- This Compound Is Well Absorbed When Taken Orally.
- It Has A Half-life Of 5–7 Days
- Excreted Primarily In The Urine.
- It Exhibits Significant Protein Binding And Enterohepatic Circulation
- Distributed To Adipose Tissues.

Mechanisms of Action

- Binds To Er Alpha, Er Beta
- Act As Pure Estrogen Antagonist In All Human Tissues
- Action At The Hypothalamic Level
- The Amount Of LH/FSH Released In Each Secretary Phase Is Increased

Clomiphene - MoA




Clomiphene citrate
Hypothalamus
GnRH
Estrogens
Pituitary gland
Ovary
LH/FSH

Clinical uses

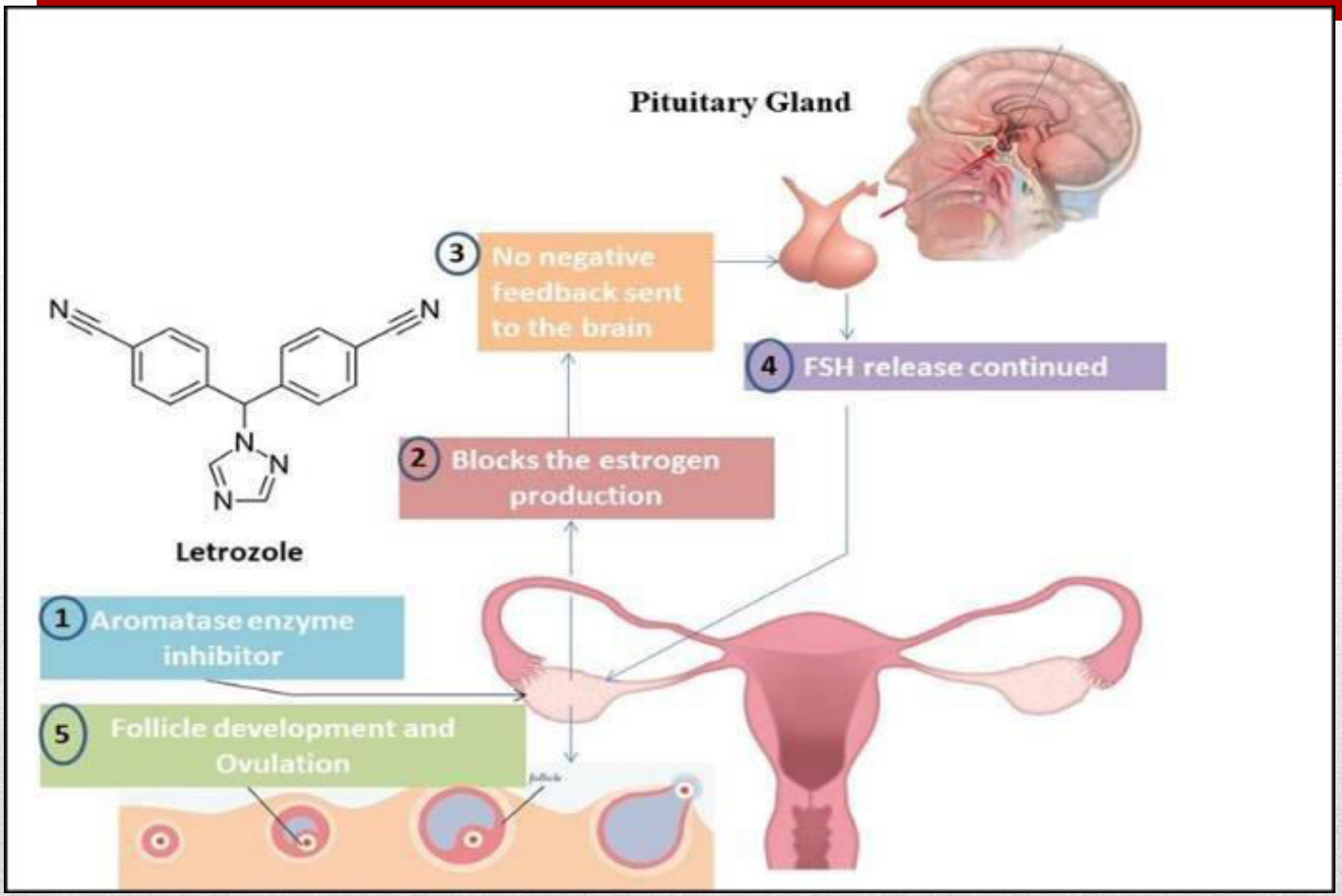
- Infertility due to anovulation.
  - 50-100mg per day od for 5 days
  - Starts on 3rd day of cycle
  - Cyclical therapy is recommended but not more than 6 cycle as increase chances of ovarian cancer.
- Male infertility for
  - oligospermia promote Spermatogenisis
  - Testosterone Secretion
- Assisted reprodution therapy (ART) & gametes intrafallopian transfer technique (GIFT).

Clomiphene

- DOSE
  - 50mg/day starting from day 3-7 for 2 months
  - then double the dose 50mg BD for 3 months
  - maximum 200mg/day can be given
- Addition Of Hcg Inj On Day 13 Or 14 Improves Success Rate
- IN OLIGOSPERMIA DOSE IS
  - 25mg/day for 24 days in a month, 6 days rest up to 6 months

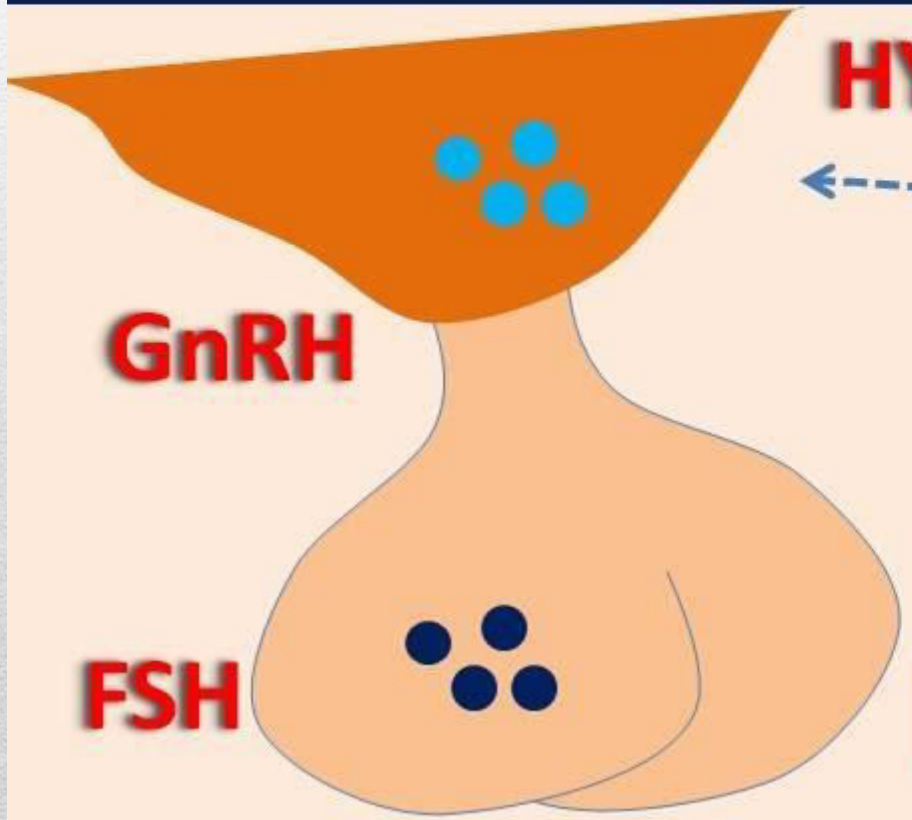
Adverse Effects

- Hot Flushes (Antagonism Of Peripheral Actions Of Estrogen)
- Gastric Upsets nausea vomiting
- Hyperstimulation syndrome. Polycystic Ovaries
- Multiple Pregnancy
- Ovarian cysts
- Allergic Dermatitis
- Risk Of Ovarion Tumours
- Weight gain breasts discomfort


Pituitary Gland
3 No negative feedback sent to the brain
4 FSH release continued
2 Blocks the estrogen production
Letrozole
1 Aromatase enzyme inhibitor
5 Follicle development and Ovulation

letrozole

LETROZO



HYPOTHALAMUS

GnRH

PITUITARY

FSH

LETROZOLE

ANDRO

ANTI-ANDROGENS
Male Contraception

Anti-androgens list

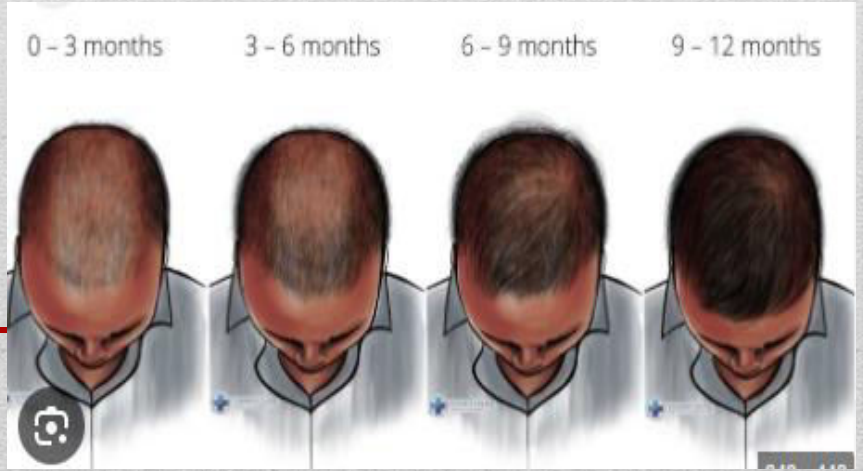
- Steroid Synthesis Inhibitors
  - Ketoconazole
- Conversion of Steroid Precursors of Androgens
  - Abiraterone
  - Finastride
  - Dutasteride
- Receptor Inhibitors
  - Cyproterone and cyproterone acetate
  - Flutamide, Bicalutamide and nilutamide
- Spironolactone

Antiandrogens

- Ketokonazole
  - Antifungal
  - inhibitor of adrenal and gonadal steroid synthesis
  - Not clinically useful in women with increased androgen levels bc of the toxicity with prolong use
  - Not useful in prostatic carcinoma

CONVERSION OF STEROID PRECURSORS TO ANDROGENS

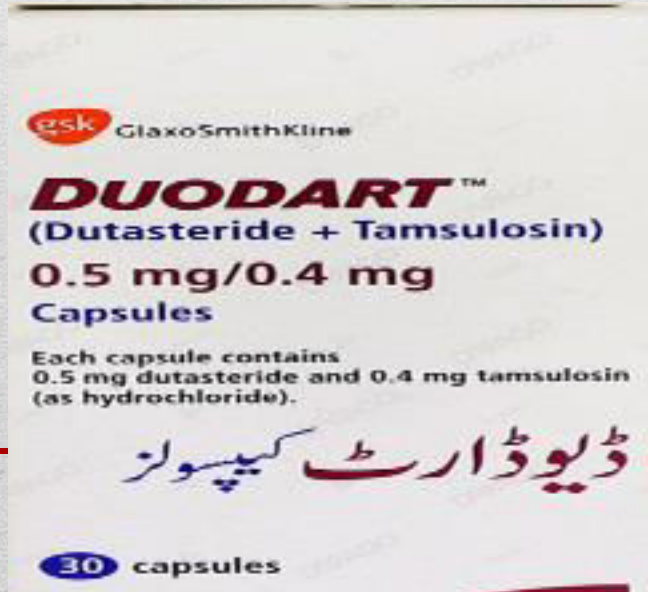
- Finasteride, inhibitor of 5αreductase enzyme,
  - orally active and causes a reduction in DHT levels
  - begins within 8 hours after administration
  - lasts 24 hours
  - Effective in reducing prostate size BPH
  - The dosage is 5 mg/d.
  - Also successfully in the Rx of HIRSUTISM in women
  - And early male pattern baldness in men.



CONVERSION OF STEROID PRECURSORS TO ANDROGENS

Dutasteride

- orally a much longer half-life than finasteride.
- dosage is 0.5 mg daily.
- These drugs are not approved for women or children,



- Abiraterone
  - a newer 17-hydroxylase inhibitor, may prove to be clinically successful
  - Used in prostate cancers

CONVERSION OF STEROID PRECURSORS TO ANDROGENS

Receptor Inhibitors

- **Cyproterone**
  - Effective anti-androgens
  - Inhibit the action of androgens at the target organ.
  - Suppresses the feedback enhancement of LH & FSH,
  - In combination with estrogen, for the therapy of severe acne and hirsutism in females.
  - In men to decrease excessive sexual drive
  - Palliative in prostatic carcinoma,

Receptor Inhibitors

- **Flutamide,**
  - is a potent antiandrogen
  - Non-steroid, a competitive antagonist at the androgen receptor.
  - mild gynecomastia (probably by & mild reversible hepatic toxicity.
  - used in the treatment of prostatic carcinoma.
  - management of excess androgen effect in women

- **Bicalutamide and nilutamide**
- potent orally active antiandrogens
- single daily dose
- used in patients with metastatic carcinoma of the prostate.
- Bicalutamide in combination with a GnRH analog to reduce tumor flare

Receptor Inhibitors

- Spironolactone,
  - Competitive inhibitor of Aldosterone
  - Also competes with dihydrotestosterone receptors in target tissues.
  - It also reduces 17α-hydroxylase activity, lowering plasma levels of testosterone and androstenedione.
  - 50–200 mg/d is used the for hirsutism in women.
  - As effective as Finasteride, Flutamide, Or Cyproterone in this condition

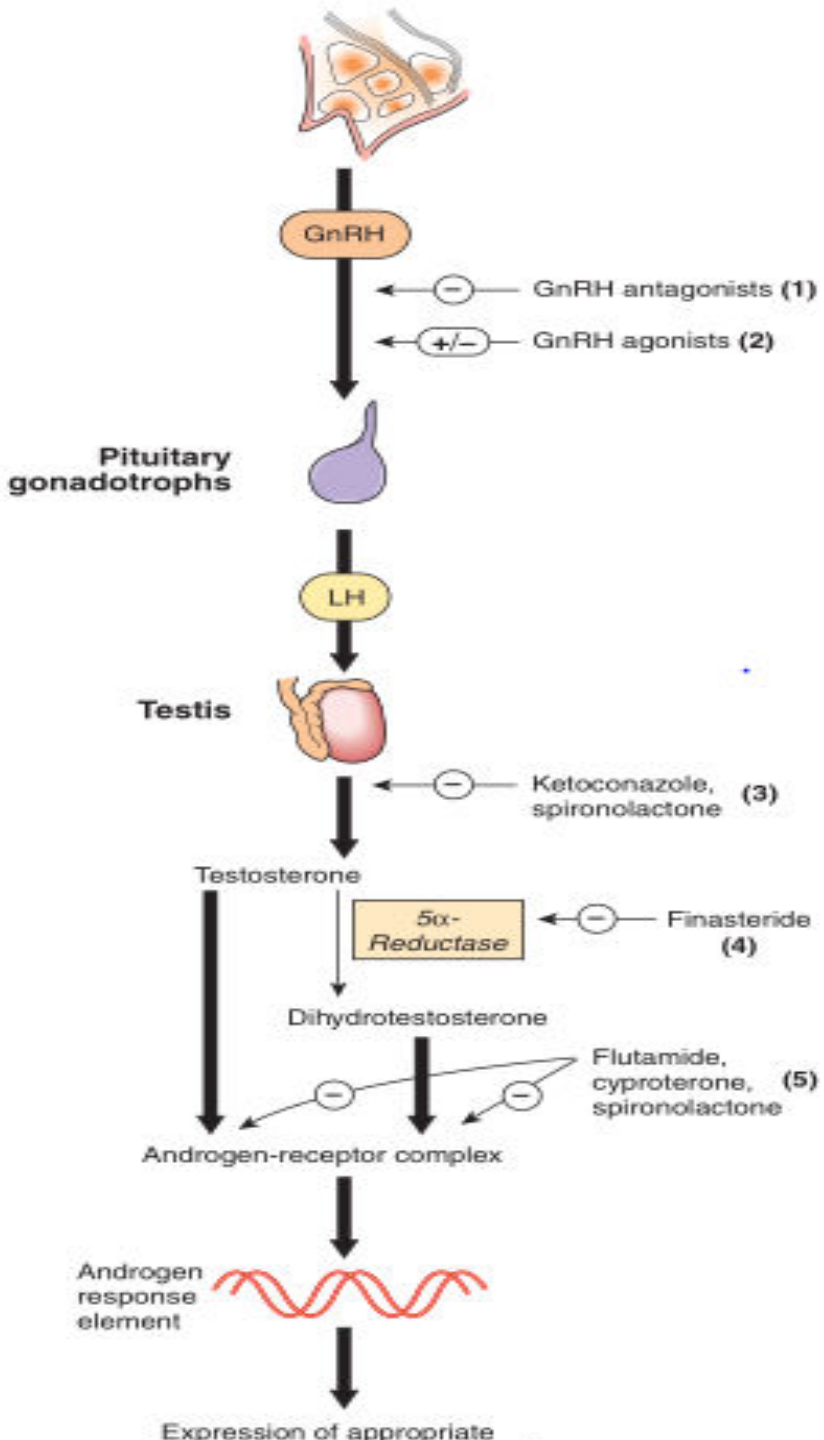


FIGURE 40–6 Control of androgen secretion and activity and some sites of action of antiandrogens: **(1)** competitive inhibition of GnRH receptors; **(2)** stimulation (+, pulsatile administration) or inhibition via desensitization of GnRH receptors (–, continuous administration); **(3)** decreased synthesis of testosterone in the testis; **(4)** decreased synthesis of dihydrotestosterone by inhibition of 5α-reductase; **(5)** competition for binding to cytosol androgen receptors.

To Summarize

CHEMICAL CONTRACEPTION IN MEN

- No effective oral contraceptive for men.
- e.g , various androgens, i.e. testosterone & testosterone enanthate,400 mg per month, produced azoospermia in < ½ of cases treated.
- Minor adverse reactions, including gynecomastia and acne.
- Testosterone in combination with danazol was well tolerated but no more effective than testosterone alone

GOSSYPOL

- cotton seed derivative
- Trial conducted in china
- This compound destroys elements of the seminiferous epithelium but does not significantly alter the endocrine function of the testis.
- 20 mg/d of gossypol or gossypol acetic acid for 2 months, followed by a maintenance dosage of 60 mg/wk.
- On this regimen,99% of men developed sperm counts below 4 million/mL.

GOSSYPOL

- Hypokalemia is the major adverse effect and may lead to transient paralysis
- gossypol has been abandoned as a candidate male contraceptive.


THANK YOU!