Drugs used in male infertility

Objectives:

- **Define** male infertility
- **Recognize** regulations contributing to male fertility & dysregulations leading to infertility
- **Classify** hormonal & non-hormonal therapies used in male infertility whether being empirical or specific.
- **Expand** on the mechanism of action, indications, preparations, side effects, contraindications & interactions of most hormonal therapies
- **Highlight** some potentialities of empirical non-hormonal therapies

Done by:

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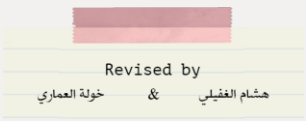
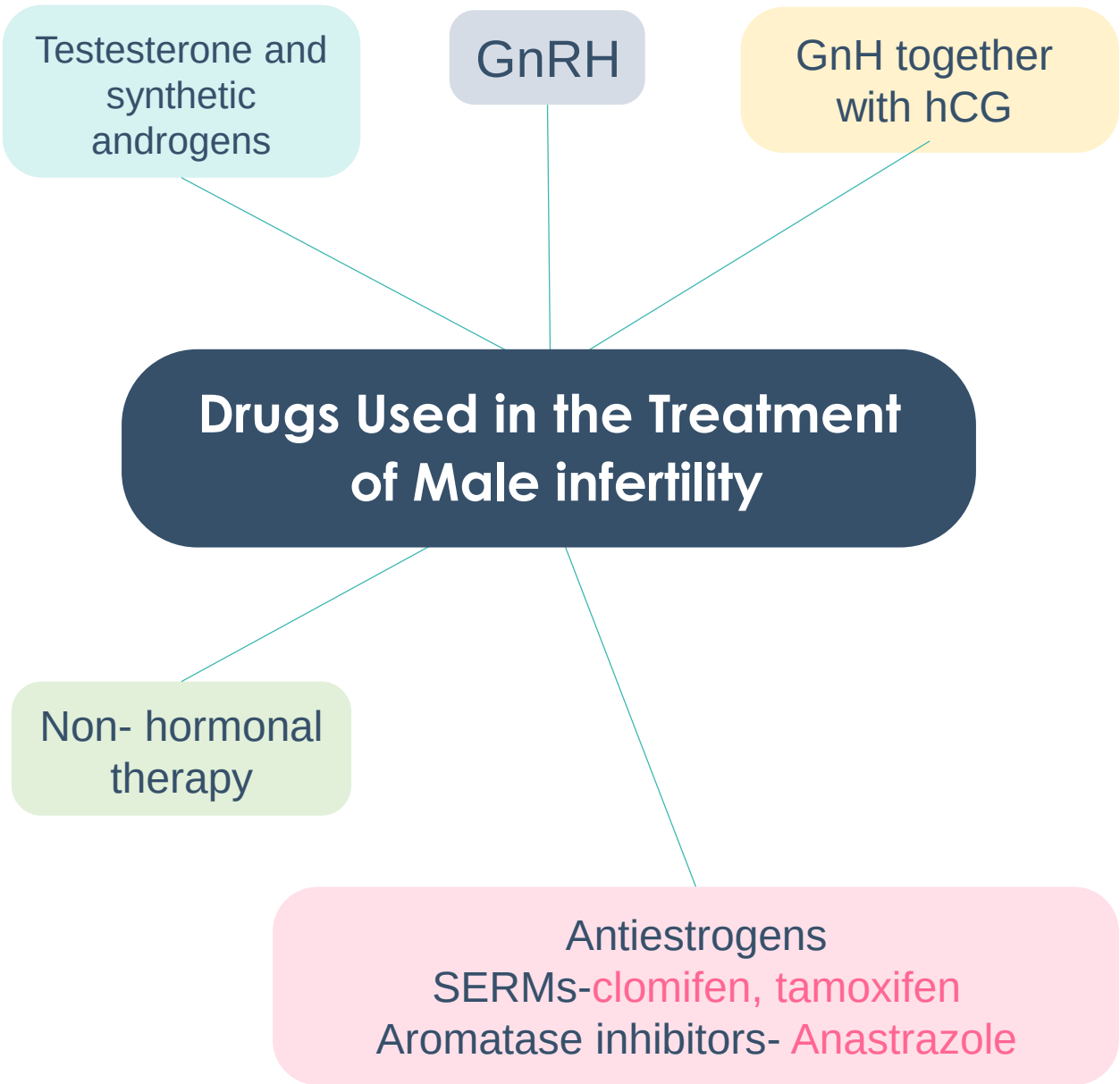


« قل سيروا في الأرض فانظروا كيف بدأ الخلق »

سورة العنكبوت

Mind Map



إذا ضاق الوقت عليكم وما قدرتوا تدرسون هالمحاضرة، أهم شيء مروا على سلايد ٧ و ٨ (**المستطيلات الصفراء**)، اللي هم دواء Anastrazole و Mesterolone والمعلومات المتعلقة بهم.

To Understand Better | Male Infertility

Definition of male infertility

Inability of a male to achieve **conception** in a fertile woman after **one year** of **unprotected** intercourse.

Prevalence

Infertility has traditionally been thought of as a woman's problem. However, about one of every three cases of infertility is due to the man alone.

What is the difference between Infertility vs Impotence?

- **Infertility**: the male sexual behavior is fine but the problem in the sperms (low count, abnormal shape , abnormal motility)
- **Impotence**: the male has problem in his sexual behavior (Erectile Dysfunction)
- **In male infertility, the semen analysis is abnormal:**
  - Count is low (**oligo**spermia)
  - Sperms are absent in the ejaculate (**azoo**spermia)
  - Sperm motility is seriously affected (**astheno**spermia)
  - Sperms are totally immobile or dead (**necro**spermia)

Physiology revision: Helpful diagram

1. Pulsatile secretion of GnRH from hypothalamus will stimulate anterior pituitary to secrete gonadotropin **(FSH , LH)** that will lead ➔ initiation & maintenance of spermatogenesis:
2. **FSH:** will act on sertoli cell in seminiferous tubule lead to release inhibin ➔ (negative feedback on anterior pituitary)
3. Cconvert testosterone in seminiferous tubule to **dihydrotestosterone (DHT)** and **Estradiol ➔ (** positive feedback on leydig cells and negative feedback on anterior pituitary, hypothalamus)
4. **LH:** will act on leydig cell lead to secrete testosterone ➔ (negative feedback on anterior pituitary and hypothalamus)
5. Note:
   - LH ➔ Testosterone in a **pulsatile** manner
   - (chronic LH➔ makes testis refractory)

Male infertility

Causes of male infertility

Pre-Testicular:
(Problems related to hormone production)

(Poor hormonal support & poor general health)

including:
- Hypogonadism
- Drugs
- Alcohol
- Tobacco
- Strenuous riding (bicycle & horse riding)
- Medications (chemotherapy , anabolic steroids)

Testicular:
(Problems related to sperm production

(Testes produce semen of low quantity and/or poor quality)

Including:
- Age
- Malaria
- Testicular cancer
- Idiopathic (unexplained sperm deficiencies)

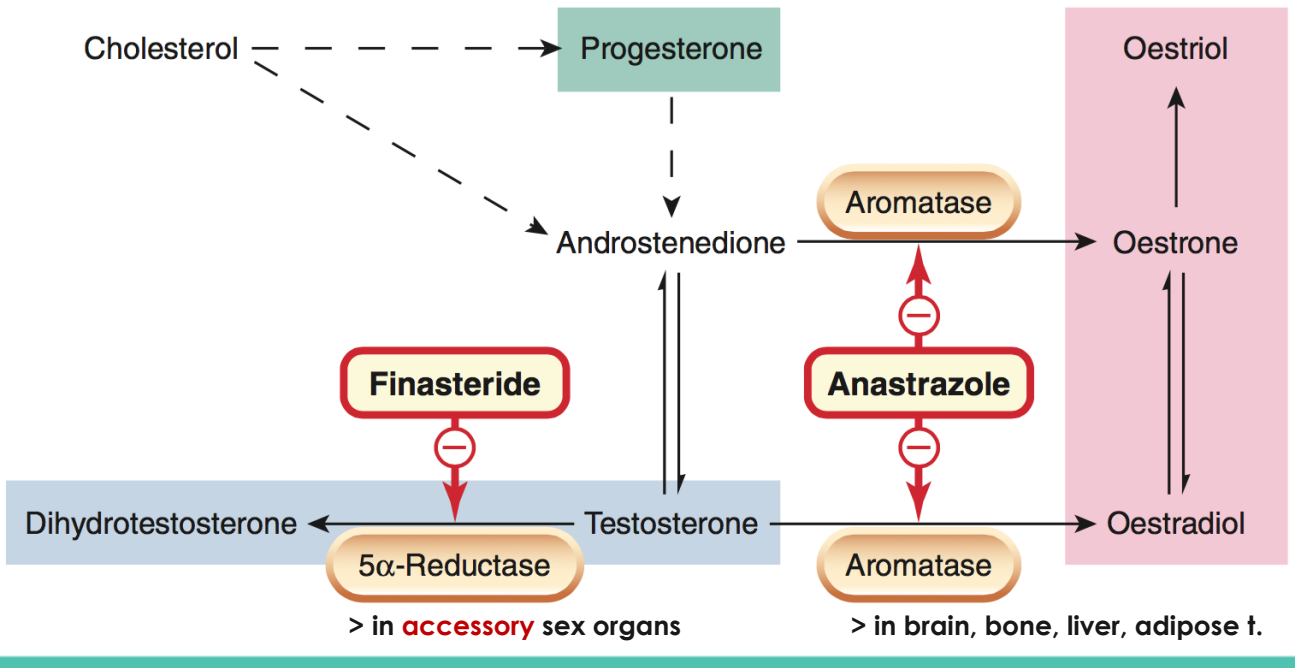
Post-Testicular:
(Problems related to sperm transport, **erection** or **ejaculation**)

(Conditions that affect male genital system after sperm production)

Including:
- Vas deferens obstruction
- Infection e.g. : prostatitis, T.B.
- Ejaculatory duct obstruction
- impotence

Important: 25% of cases are idiopathic.

❖ The biosynthetic pathway for the androgens and oestrogens



Drug treatment of male infertility

(changes appear after 3 months)

Drug

A. Hormonal Therapy

Specific

- Hyperprolactinemia → **DA_2- Agonists**
- Hypothyroidism → **Thyroxine**
- Congenital Adrenal Hyperplasia → **corticosteroids**
- Glucocorticoids excess → correct levels

Empirical

- **Idiopathic** → Androgens, Anti-estrogen (SERMs & aromatase inhibitors), GnH (**FSH**).
- **Euogonadotrophic Hypogonadism** → (↓T "testosterone" only) → Anti-estrogens (SERMs & Aromatase Inhibitors).
- **Hypogonadotrophic hypogonadism** → **2ndry** Hypogonadism (Hypothalamo-Pituitary) (↓ FSH / LH & ↓T) → treat with Pulsatile GnRH, hMG , hCG, Androgens, Clomiphene.
- **Hypergonadotrophic Hypogonadism** (Testicular dysfunction) → **1ry** Hypogonadism (↑LH & ↓T) → treatment: Assisted Reproduction (تخصيب خارجي) (no other treatment until now)

B. Non-Hormonal Therapy

Specific

- **Erectile Dysfunction** → **PDE5 inhibitors** e.g. Sildenafil (Viagra), Vardenafil (Levitra), Tadalafil (Cialis).
- **Premature Ejaculation** → SSRI (e.g. Prozac)
- **Infection** of testes, prostate & UTI → Antibiotics

Empirical

- Kallikrein
- Antioxidants; e.g. vit.E, vit.C
- **Zinc Supplements**.
- Folic acid.
- L-Carnitine.

Drugs used in treatment of male infertility

1- Testosterone and synthetic androgens

2- Antiestrogens

SERMs e.g. clomifen, tamoxifen

Aromatase inhibitors e.g. Anastrazole

3- GnRH (hypothalamic amenorhea)

4- GnH together with hCG (pituitary failure)

5- Non-hormonal therapy (antioxidants, zinc,folic acid, etc.)

✓ Anastrazole is the most imp drug in this lecture!

1-Testosterone

Principle male sex hormone produced in testis (> 95%), small amount in adrenals.
It follows a **circadian pattern** → ↑ in early morning & ↓ in evening

Mech. of action

A. Prostate and seminal vesicles:

- Testosterone is converted by **α-reductase** to DHT
- Testosterone is converted in **accessory sex organs** (prostate and seminal vesicles) by **5-alpha reductase** to DHT → it effects proteins → gives androgenic effect.

B. Bones and brain:

- Testosterone is metabolized to **estradiol** by **c-p450 aromatase**.
- **Bones**: estradiol accelerates **maturation of cartilage into bone** leading to closure of the epiphysis & conclusion of growth.
- **Brain**: estradiol serves as the **most important feedback signal to the hypothalamus** (esp. affecting LH secretion).

Pharmacological effects

❖ Virilizing effects

- Gonadotropin regulation.
- Spermatogenesis.
- Sexual dysfunction (if used in excess amount)
- Sexual restoration and development (in case of decreased testosterone)

❖ Protein anabolic effects:

- ↑ bone density.
- ↑ muscle mass.
- ↑ red blood cell mass.

→ (That's why body builders use it)

Note:
★ Testosterone and synthetic androgens has **both** virilizing and protein anabolic effect.
★ Anabolic steroid has only protein anabolic effect → not used in infertility.

P.K

- **Ineffective orally** (inactivated by 1st pass metabolism) → given **I.M or S.C.** (Skin patch & gels are also available)
- Binds to **Sex Hormone Binding Globulin** [SHBG]
- $T_{1/2}$ = 10 –20 min
- Inactivated in the liver; 90% of metabolites → excreted in urine.
- **Disadvantages**: Rapidly absorbed, rapidly metabolized (**Short duration of action**).

عشان نتجنب مساوئ synthetic androgen بيقى إحنا بنستخدم natural androgenال

❖ Synthetic androgens:

- Less rapidly metabolized & more lipid soluble → increasing its duration of action.

❖ **Derived from Testosterone:**

- **Esters**: propionate, enanthate, cypionate → in oil for **I.M**; every 2-3 weeks. زي ما قلت لكم الdose & interval مش حطلبها منكم
- **Other derivatives** as: Fluoxymesterone, Methyltestosterone, Danazol → given **Orally**; daily.

❖ **Derived from DHT:**

- **Mesterolone** مهم!! → given **Orally**; **daily**.

(you should remember each one is derived from what & if its given orally or I.M)

1-Testosterone (cont.)

ADRs

- **Excess androgens** (if taken > 6 weeks) can cause **impotence**, decreased spermatogenesis & gynecomastia.
- **Alteration in serum lipid profile**: ↓HDL & ↑ LDL, hence, ↑ risk of premature coronary heart disease.
- Salt & water retention → **edema**.
- **Hepatic dysfunction**: ↑ AST levels, ↑ alkaline phosphatase, ↑ bilirubin & cholesteric jaundice.
- **Hepatic carcinoma** (long term use)
- Polycythemia (↑ number of RBC) → ↑ risk of clotting.
- Behavioral changes: physiologic dependence, ↑ aggressiveness, psychotic symptoms.
- **Premature closing of epiphysis of the long bones**.
- Reduction of testicular size.

Indications

❖ **As Testosterone Replacement Therapy (TRT):**

- Therapy for androgen deficiency in adult male infertility.
- In **delayed puberty** with hypogonadism → give androgen slow & spaced for fear of **premature fusion of epiphyses** → short stature.

C.I

- Male patients with breast or prostate cancer.
- Severe renal & cardiac disease → predispose to **edema**
- Psychiatric disorders
- **Hypercoagulable states**
- Polycythemia

Interactions

- With **corticosteroids** → edema (testosterone potentiates corticosteroid effect)
- With **warfarin** → ↓ warfarin metabolism → **bleeding**
- With **insulin or oral hypoglycemics** → **hypoglycemia**
- With **propranolol** → ↑ **propranolol** clearance → ↓ its efficacy

يزيد قوة الكورتيكوستيرويد والوارفارين والإنسولين، أما بروبرانولول يقلل فعاليته

مهم مرة!!

Mesterolone: (synthetic androgen derived from DHT, given orally, derived from DHT)
More safely given in case of **decreased testosterone** or in **2ndry hypogonadism**. **Why?**

1. **Not aromatized into estrogens** → no negative feedback on GnHs → encourages **natural** testosterone production → spermatogenesis is enhanced.
2. Unlike other oral synthetic androgens, it is **not hepatotoxic.**

2- Anti-Estrogens

Because estrogens → have **negative feedback** on hypothalamus → ↓ GnRH pulse frequency & pituitary responsiveness to GnRH, so antiestrogens → ↑ GnRH & improve its pituitary response.

Types

A. SERM:
Tamoxifen, Clomiphene
✓ Both drugs can induce libido & bad temper in men.

B. Aromatase Inhibitors: Anastrozole مهم جدًا!!
✓ **Blocks conversion of testosterone to estrogen within the hypothalamus**

- All are used for inducing spermatogenesis in oligozoospermia (count is low)
- Given as daily dose over a period of 1–6 months.
- Best to improve sperm count & motility with good pregnancy rates.

Anastrazole, عبارة عن واحد أخذ MCQsمعظم ال
.. which of the following explain its MOA?

3- GnRH

- **Used in hypothalamic dysfunction** المشكلة في الهايبوثالمس
- Given as Pulsatile GnRH therapy (4-8 ug subcut every 2 hours) using a portable pump.
- Exogenous excess of GnRH → down-regulation of pituitary GnRH receptors & ↓ LH responsiveness.

ADRs

- Headache, Depression.
- Generalized weakness, Pain.
- Osteoporosis, **Gynecomastia**.

ما فيش حاقة specific عشان كدا مافيش حاقة أسألكم فيها

4- GnHs

- Used in **2ndry hypogonadism** (absent FSH or absent FSH & LH) → ↑ spermatogenesis
- GnHs replacement must be combined; hCG (**I.M**. → 2 ms.) followed by hCG + hMG (**I.M**. → 6 -12 ms). العلاج ممكن يستمر لمدة طويلة

ADRs

- Headache, Depression.
- Local swelling (injection site)
- Flushing, Nausea.
- Precocious puberty ،Gynecomastia.

5- Non-HORMONAL THERAPY

Antioxidants	FOLIC ACID	ZINC	L-CARNITINE	KALLIKREIN
Protect sperm from oxidative damage (e.g. vit **E, C**)	Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties.	Plays an important role in testicular development, sperm production & sperm motility.	Highly concentrated in the epididymis & Is **important for sperm maturation**.	Has proteolytic activity, cleaving **kininogen to kinins** حركة important for sperm motility.

Summery-1

1-Testosterone

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Summery-2

C.I

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- Psychiatric disorders
- Hypercoagulable states
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ADRs

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Depression.
Generalized weakness.
Pain.
Osteoporosis.
Gynecomastia.

4-GnHs

Used in 2ndry hypogonadism (absent FSH or absent FSH & LH) →↑ spermatogenesis
hMG combined with hCG.

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MCQs

1- Inability of a male to achieve conception in a fertile woman after one year of unprotected intercourse, is the definition of :
A- Conception.
B- Infertility.
C- Intercourse.
D- Impotence .

2- The cause of male infertility is idiopathic in :
A- 75% of cases.
B- 95% of cases.
C- 25% of cases.
D- 50% of cases.

3- Which of the following is a post testicular cause of male infertility :
A- Vas deferens obstruction.
B- Alcohol.
C- Age.
D- Malaria.

4- Which of the following is a virilizing effect of Testosterone :
A-Increase bone density.
B-Increase muscle mass.
C-Increase red blood cell mass.
D- Spermatogenesis.

5- The most important deference between Testosterone and synthetic androgen is :
A- Virilizing effects.
B- Anabolic effects.
C- Binds to Sex Hormone Binding Globulin.
D- Duration of action.

6- If Testosterone and Warfarin are used together, which of the following effects might occur :
A- Edema.
B- Bleeding.
C- Hypoglycemia.
D- Hepatic toxicity.

7- Which of the following drugs inhibits the conversion of testosterone to estrogen?
A- Clomiphene.
B- Anastrozole.
C- Mesterolone.
D- Kallikrein.

Answers: 1-B 2-C 3-A 4-D 5-D 6-B 7-B

Thank you for checking our team!

Pharmacology 435

@ pharmacology435

Sources:

1. 435's slides.