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Drugs used in infertility

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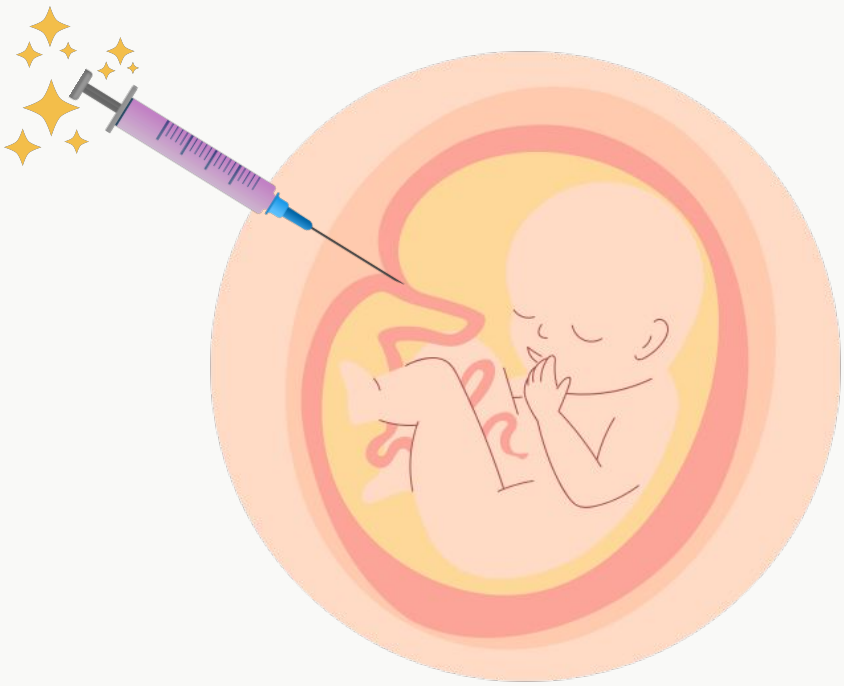


- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

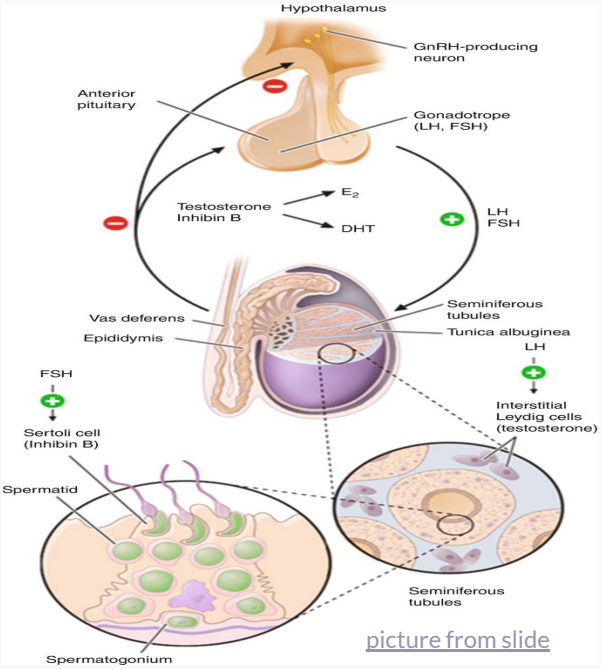
EDITING FILE

Objective

- 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.

Male infertility

Definition	Inability of a male to achieve conception in a fertile woman after one year of unprotected intercourse.
Prevalence	• Approximately 15-20% of all couples are infertile • In up to 50% of such cases (7.5-10%), males are responsible
semen analysis	In male infertility, the semen analysis is abnormal: • Count is low *(oligospermia)* • Sperms are absent in the ejaculate *(azoospermia)* • Sperm motility is seriously affected *(asthenospermia)* • Sperms are totally immobile or dead *(necrospermia)*
Infertility vs Impotence	**Impotence**: another word for erectile dysfunction difficulty getting or keeping an erection. **Infertility**: inability to produce or release sperms.



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Pre-testicular

Problems related to hormones production

LH,FSH initiate & maintain the spermatogenesis

Estrogen facilitate the -ve of testosterone on GnRH & GnHs

testicular

Problems related to sperm production

Post-testicular

Problems in Erection & Ejaculation + sperm transport

- LH → Testosterone → Pulsatile Manner
- Chronic LH → makes testis refractory

Causes of male infertility

Idiopathic	25% (causes unknown).
Pre- testicular causes	**Poor hormonal support & general health including:** • Hypogonadism • Drugs • Strenuous riding (bicycle & horse riding) • alcohol • Tobacco • Medications (chemotherapy, anabolic steroids).
Testicular causes	**Testes produce semen of low quantity and/or poor quality:** • Age • Malaria • Testicular cancer; etc.
Post-testicular causes	**Conditions that affect male genital system after testicular sperm production:** • Vas deferens obstruction • Infection, e.g. prostatitis, T.B • Ejaculatory duct obstruction • Impotence.

Treatment of male infertility

Drug treatment of male infertility

- Hormonal therapy
  - Specific
  - Empirical
- Non-hormonal therapy
  - Specific
  - Empirical

The treatment needs 3 months before semen quality changes

Hormonal Therapy

Specific		Empirical	
Causes	**Treatment**	**Cause**	**Treatment**
Hyperprolactinemia	D2- Agonists (Bromocriptine)	**Idiopathic**	-Androgens -Antiestrogen -GnH (FSH)
Hypothyroidism	Thyroxine	**Eugonadotropic hypogonadism** ↓Testosterone Only, normal FSH & LH	-Antiestrogens: -SERMs -Aromatase inhibitors
Congenital Adrenal Hyperplasia	Corticosteroids	**Hypogonadotropic hypogonadism:** -2ndry Hypogonadism (Hypothalamo-Pituitary) -↓testosterone &↓ FSH / LH	-Pulsatile GnRH -hCG / hMG -Androgens -Clomiphene
Glucocorticoids excess	Correct levels	**Hypergonadotropic hypogonadism:** -Testicular dysfunction (1ry Hypogonadism) -↓testosterone &↑ LH	Assisted Reproduction (no treatment)

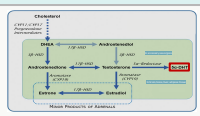
Non-hormonal therapy

Specific		Empirical
Cause	**Treatment**	
Erectile dysfunction	PDE5* inhibitors: -sildenafil (viagra) -vardenafil(levitra) -tadalafil (cialis)	• **Antioxidants; e.g. vit. E, vit. C** • **Zinc Supplements** • **Folic acid** • **L-Carnitine**
Premature Ejaculation	SSRIs (e.g.fluoxetine "Prozac")	
Infection of testes, prostate & UTI	Antibiotics – some antibiotics can cause oligospermia	

PDE5, Phosphodiesterase type 5
SSRI, Selective serotonin reuptake inhibitors

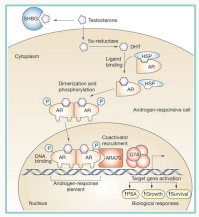
Testosterone & Synthetic Androgens

Intro



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

M.O.A



- In **prostate & seminal vesicles:** Testosterone is converted by 5α-reductase to the more potent androgen dihydrotestosterone (DHT – active form of testosterone)
- In **Bones & Brain:** Testosterone is metabolized by CYP450 aromatase to estradiol
  - ➔ **Bones:** Estradiol accelerates maturation of cartilage into bone → closure of the epiphysis & conclusion of growth.
  - ➔ **Brain:** Estradiol serves as the most important -Ve feedback signal to the hypothalamus (esp. Affecting LH secretion).

Effect

1. Virilizing Effects: (male characters)

- Gonadotropin regulation
- Spermatogenesis
- Sexual dysfunction "if increased"
- Sexual restoration and development

2. Protein anabolic effects: (Anabolic steroids: unapproved use)

3 ↑: ○ Increased bone density ○ Increased muscle mass ○ Increased RBCs mass

P.K.

Ⓞ **Natural Androgens:**

- Ineffective orally (inactivated by 1st pass met.)→ I.M, S.C., Skin patch & gels are also available
- Inactivated in the liver; 90% of metabolites → excreted in urine.
- Binds to Sex Hormone Binding Globulin (SHBG), t1/2 = 10 –20 min
- Disadvantages: Rapidly absorbed & metabolized (short duration of action).

Ⓞ **Synthetic Androgens:**

- Less rapidly metabolized & more lipid soluble→ ↑ its duration of action.
- Derived from Testosterone:
  - ➔ Esters; Propionate, Cypionate→ in oil for IM; every 2-3 weeks.
  - ➔ Other derivatives as Methyltestosterone, Danazol→ given Orally; daily.
- Derived from DHT: Mesterolone→ given Orally; daily.
  - ➔ Mesterolone Indication: ↓Testosterone & 2ry hypogonadism
    More safe than other synthetic androgen, **because:**
    1. Not aromatised into estrogens → no -ve feedback of GnHs → encourages natural testosterone production → spermatogenesis is enhanced.
    2. Unlike other oral synthetic androgens it is Not Hepatotoxic.

Indications

Of **Testosterone Replacement Therapy (TRT):**

- Therapy for androgen deficiency in adult male infertility.
- In delayed puberty with hypogonadism: Give androgen slow & spaced to minimise the risk of premature fusion of epiphyses → Short stature.

ADRs

- Excess androgens (if taken>6w) → impotence, ↓ spermatogenesis & gynecomastia.
- Alteration in serum lipid profile: ↓HDL & ↑LDL, hence, ↑risk of premature coronary heart disease
- Polycythemia (↑ no. of RBCs)→ ↑ risk of clotting.
- Salt & water retention → edema.
- Hepatic dysfunction; ↑ AST levels, ↑ ALT, ↑ bilirubin & cholestatic jaundice.
- Hepatic carcinoma (long term use).
- Behavioral changes; physiologic dependence, ↑aggressiveness.
- Premature closing of epiphysis of the long bones.
- Reduction of testicular size.

#

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

Drug Interaction

- Corticosteroids → edema.
- Warfarin→ ↓ metabolism→ ↑ bleeding.
- Insulin or oral hypoglycemics→ hypoglycemia.
- Propranolol→ ↑ propranolol clearance→ ↓ efficacy.

AntiEstrogen

Class	**Selective Estrogen receptor modulator (SERMs)**	**Aromatase Inhibitors**
Drugs	**Tamoxifen, Clomiphene**	**Anastrozole**
M.O.A.	Because estrogens have **-ve feedback** on the hypothalamus→ ↓GnRH pulse & pituitary responsiveness to GnRH, so antiestrogens→ ↑ GnRH & improve its pituitary response.	
	-	Blocks conversion of testosterone to estrogen within the hypothalamus
Uses	All are used for inducing spermatogenesis when sperms count is low.	
ADRs	Both drugs can induce libido & bad temper in men.	-

Gonadotropin Releasing Hormone (GnRH)

Uses	Hypothalamic dysfunction (Hypothalamic amenorhea).
P.K	○ Given as Pulsatile GnRH therapy using a portable pump. ○ Exogenous excess of GnRH → down-regulation of pituitary GnRH receptors & ↓ LH responsiveness"Desensitization".
ADRs	○ Headache & Pain ○ Depression & generalized weakness ○ Gynecomastia ○ **Osteoporosis**.

Gonadotropin Hormones (GnHs)

Uses	○ 2ndry hypogonadism (FSH or both FSH & LH absent) → ↑ spermatogenesis. ○ hMG combined with hCG. ○ GnH together with hCG→ treat pituitary failure. hMG, Human Menopausal Gonadotrophin; hCG, Human Chorionic Gonadotrophin
ADRs	○ Headache ○ Local swelling (injection site) ○ Nausea ○ Flushing ○ Depression ○ Gynecomastia ○ Precocious puberty.

Non-Hormonal Therapy

Sometimes is very promising, to improve sperm **quality** and **quantity**.

Antioxidants	○ Protect sperm from oxidative damage. "ROS may affect sperm quality" ○ e.g. vitamin E & C
Folic Acid	○ Plays a role in RNA and DNA synthesis during spermatogenesis ○ Has antioxidant properties.
Zinc	Plays an important role in: ○ testicular development ○ sperm production ○ sperm motility.
L-carnitine	○ Highly concentrated in the epididymis ○ Important for sperm maturation and motility.

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