Pharmacology 439

MED439

pharmacology Team 438

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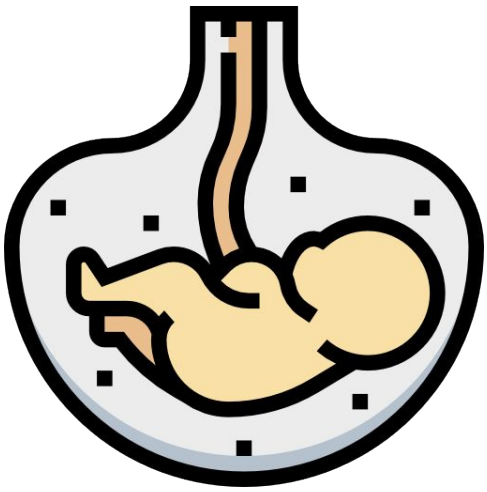


Reproduction Block

Pharmacology team 439

Drugs Used in Males Infertility

Objectives:

By the end of the lecture , you should know:

- Define male infertility
- Recognize regulations contributing to male infertility & 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 non-hormonal therapies

Color index:

Black : Main content
Red : Important
Blue: Males' slides only

Pink : Females' slides only
Grey: Extra info or explanation
Yellow: Dr. notes (439)

Green: Dr. notes (438)

Male Infertility

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

Prevalence: Approximately 15-20% of all couples are infertile In up to 50% of such cases(7.5-10%), males are responsible

Infertility

The male sexual behavior is fine but the problem is in the sperm (low count, abnormal shape, abnormal motility).

VS

Impotence

The male has problems in his sexual behavior (Erectile Dysfunction)

Semen Analysis in Infertility

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)

Causes of Male Infertility

Idiopathic 25%

Unknown causes

Pre-testicular causes

(poor hormonal support & poor general health) including:

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

Testicular causes

(Problems related to sperm production):

Age, Malaria, Testicular cancer,

Post-testicular causes

(Problems of sperm transport\ erection and ejaculation):

Vas deferens obstruction, infection e.g. prostatitis, TB, Ejaculatory duct obstruction, Impotence.

Recall Hypothalamic pituitary gonadal axis

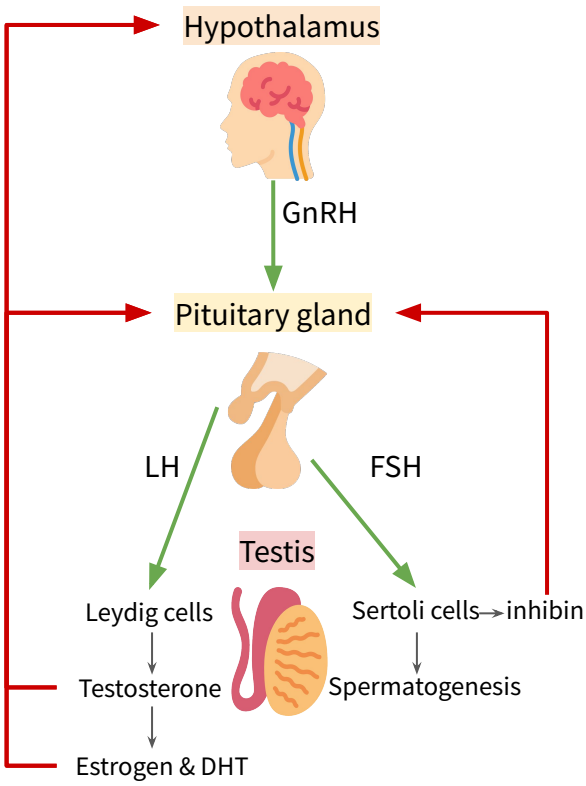
Special thanks for 436 pharmacology team

1. **Pulsatile** secretion of GnRH from hypothalamus will stimulate anterior pituitary to secrete **(FSH, LH)** that will lead to initiation & maintenance of spermatogenesis
2. **FSH:** will act on sertoli cell in seminiferous tubule for spermatogenesis. It is also release inhibin → -ve feedback on anterior pituitary
3. **LH:** will act on leydig cells leading to secretion of testosterone → -ve feedback on anterior pituitary and hypothalamus
4. Some of testosterone converted to **(DHT)** and **Estradiol** → +ve feedback on leydig cells and -ve feedback on anterior pituitary, hypothalamus

- LH releases Testosterone in a pulsatile rhythm (chronic LH levels makes testis refractory)

- **So, Drugs used to treat male infertility includes:**

1. Testosterone and synthetic androgen
2. Anti estrogen
   a. SERM e.g., clomifene (also called clomiphene), tamoxifen
   b. Aromatase inhibitors e.g., Anastrazole
3. GnRH agonists (hypothalamic amenorhea)
4. GnH together with hCG (pituitary failure)
5. Non hormonal therapy(antioxidants, zinc, folic acid, etc.)



Drug Treatment of Male Infertility

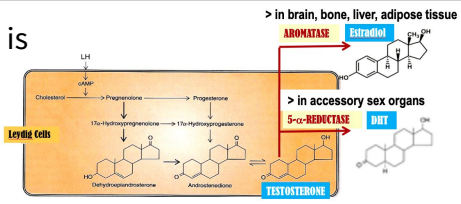
(Needs 3 months before semen quality changes)

		Causes	Treatment
Hormonal Therapy	**Specific** "We are basically just correcting the cause"	Hyperprolactinemia (Excess prolactin resulting in decreased testosterone level)	DA 2- agonists (Bromocriptine)
		Hypothyroidism	Thyroxine
		Congenital adrenal hyperplasia	Corticosteroids excess
		Glucocorticoids excess	Correct levels
	Empirical	Idiopathic	Androgens, Antiestrogen, GnH (FSH)
		Eugonadotrophic hypogonadism (↓T only) (Normal FSH & LH)	Antiestrogens (To prevent the conversion of testosterone to estrogen) (SERMs & Aromatase inhibitors)
		Hypogonadotrophic hypogonadism [secondary Hypogonadism "Hypothalamo-Pituitary"] (↓ T & ↓ FSH/LH)	(Here the cause is from the pituitary, so the first choice of drugs are FSH, and LH) Pulsatile GnRH, hCG, hMG[1], Androgens, Clomiphene, Mesterolone
		Hypergonadotrophic Hypogonadism [primary Hypogonadism "testicular dysfunction"] (↓T & ↑LH)	Assisted Reproduction (no treatment)
Non-hormonal Therapy	**Specific**	Erectile dysfunction	PDE5 inhibitors (Vasodilator) e.g. sildenafil (viagra®), vardenafil (levitra®), tadalafil (cialis®)
		Premature Ejaculation	SSRIs e.g Fluoxetine (prozac®) (small doses)
		Infection of testes, prostate & UT	Antibiotics "can cause low sperm count"
	Empirical	-	Antioxidants e.g. vit E & vit C, Zinc supplements, folic acid, L-Carnitine

1- AKA Menotropin (human menopausal gonadotropin)

★ Testosterone

We almost always start with it

Drugs	Testosterone and Synthetic androgens
info	• Principle male sex hormone produced in testis (> 95%), small amount in adrenals. It follows a circadian pattern⟶ increase in early morning & decrease in evening.
MOA	• In the prostate and seminal vesicles testosterone is converted by **5α-reductase** to **DHT**. • In bones and brain it is metabolized to **estradiol** by **c-p450 aromatase** ➔ **Bone**: 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). 
Action	1- Virilizing Effects: • Gonadotropin regulation • Spermatogenesis • Sexual dysfunction • Sexual restoration and development 2- Protein anabolic effects: (anabolic steroids: **un**approved use) • Increase bone density • Increase muscle mass • Increase red blood cell mass
P.K	"No need to know it all, only remember that we give it as IM, SC in a lipid form to increase its duration" • **Natural Androgens** ➔ **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] ➔ t1⁄2 =10–20 min ➔ Inactivated in the liver. ➔ 90% of metabolites excreted in urine. ➔ Disadvantages: Rapidly absorbed, rapidly metabolized (Short duration of action) • **Synthetic Androgens** ➔ Less rapidly metabolized & more lipid soluble ⟶ increasing its duration of action. ➔ Derived from **Testosterone**: 1. Esters, propionate,cypionate ⟶ in oil for IM (every 2-3 weeks) 2. **Other derivatives** as Methyltestosterone, Danazol⟶ given Orally (daily) ➔ Derived from **DHT** as Mesterolone: given Orally (daily) ➔ **Mesterolone**: More **safe** and can be given in ↓testosterone or in 2ndry hypogonadism; **because of the following:** 1. Not aromatised into estrogens "no –ve feedback of GnHs " encourages natural testosterone production. thus spermatogenesis is enhanced. 2. Unlike other oral synthetic androgens it is not hepatotoxic.
Uses	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). "In kids supervision is needed to control the side effects" " Of Course we don't' give testosterone to kids because of infertility, we give them for other reasons"

Testosterone Cont...

Drug	Testosterone and synthetic androgens
ADRs	1. Excess androgens (**if taken > 6 weeks**) can cause impotence, decreased spermatogenesis & gynecomastia 2. Alteration in serum lipid profile: ↓HDL & ↑LDL, hence,↑risk of premature coronary heart disease 3. Salt & water retention leading to edema 4. Hepatic dysfunction:↑AST levels,↑alkaline phosphatase,↑bilirubin & cholestatic jaundice (change to DHT to avoid) 5. Hepatic carcinoma (long term use) 6. Behavioral changes: physiologic dependence, ↑aggressiveness, psychotic symptoms 7. Polycythemia (increased number of RBC) →↑risk of clotting 8. Premature closing of epiphysis of the long bones 9. Reduction of testicular size
C.I	• Male patients with cancer of breast or prostate. • Severe renal & cardiac disease as they predispose to edema. • Psychiatric disorders. • Hypercoagulable states. • Polycythemia.
inter-Action	Monitor the dose, or stop/change one of the drugs • Testosterone + **Corticosteroids** → edema. • Testosterone ↓ **Warfarin** metabolism → ↑bleeding. • **Insulin or oral hypoglycemics** + Testosterone → hypoglycemia. • Testosterone↑ **Propranolol** Clearance → ↓Propranolol Efficacy.

Antiestrogen [1]

Class	SERMs	Aromatase Inhibitors
Drugs	**Tamoxifen** (most famous, safer)**, Clomiphene**	**Anastrozole**
MOA	• Because estrogens have -ve feedback on hypothalamus → decrease GnRH pulse frequency & pituitary responsiveness to GnRH ○ So antiestrogens → increase GnRH & improve its pituitary response.	
	• Competes with estrogen for its receptor in hypothalamus	• Blocks conversion of testosterone to estrogen within the hypothalamus.
P.K	• Given as daily dose over a period of 1–6 months.	
Uses	• All are used for inducing spermatogenesis in oligospermia (count is low). "SERMs are preferred over Aromatase, because Aromatase can cause blood clotting"	
ADRs	• Both drugs (Tamoxifen, Clomiphene) can induce libido & bad temper in men	–

1) Antiestrogen therapy is better than Androgen replacement therapy.

Other Drugs In Treating Male Infertility

Drugs	GnRH	GnHs
P.K	• 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 & decrease LH responsiveness	• GnHS replacement must combine: hCG (IM for 2 Ms.) followed by hCG + hMG "if FSH is decreased only, but mostly we give them together" (IM for 6-12 Ms.) hCG = Human Chorionic Gonadotropin hMG= human menopausal gonadotropin
Uses	• Used in **hypothalamic dysfunction**	• Used in **2ndry hypogonadism (**FSH or both FSH & LH absent) to promote spermatogenesis
ADRs	• Headache • Depression • Gynecomastia • generalized weakness • pain • osteoporosis	• Headache • Depression • Gynecomastia • local swelling (at injection site) • Nausea • Flushing • precocious puberty (not related to infertility, seen in kids)

Non-hormonal Therapy

"If it's not clear that there is a hormonal problems or idiopathic"

Antioxidants -e.g. vit E, C	Protect sperm from oxidative damage
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 & is important for sperm maturation & motility.

Quiz

MCQ

Q1- A patient with hypothalamic dysfunction is treated with GnRH, which one of the following conditions he may present with following the treatment?

A- Local swelling. B- Precocious puberty. C-Osteoporosis. D- Polycythemia.

Q2- L-carnitine is important for:

A- Sperms motility B- Sperms protection C- Sperms production D- Sperms maturation

Q3- Which of the following oral synthetic androgens is not hepatotoxic ?

A- Fluoxymesterone. B- Mesterolone. C- Methyltestosterone. D- Danazol.

Q4- A patient is using Anastrozole for treating oligospermia, Which one of the following is the mechanism of action of this drug?

A- DA-2 agonist
B- Phosphodiesterase-5 inhibitor
C- Blocks conversion of testosterone to estrogen within the hypothalamus
D- Selective Serotonin Reuptake Inhibitor

SAQ

- 27-years-old man married 2 years ago visit the clinic due to inability to conceive, doctor order hormonal profile for patient and the results from lab shows decreased (testosterone,FSH ,LH).

Q1-Which drug would be effective in treating infertility due to hypothalamic dysfunction?
Q2-Mention 2 ADR of that drug?

- 35-years-old male visit the clinic due to inability to conceive after investigation it turns out that he has infertility due to abnormal sperm motility.

Q3-Which non-hormonal drug should he used in this case?
Q4-What is the M.O.A of that drug?

- If Testosterone and Warfarin are used together, What is the effect that might be occur?

Answers:

MCQ

Q1	C
Q2	D
Q3	B
Q4	C

SAQ

Q1	Pulsatile GnRH
Q2	Gynecomastia - pain
Q3	Kallikrein
Q4	Has proteolytic activity, cleaving kininogen to kinins
Q5	Bleeding

Thank you for all the love and support you gave the team in those two years!

Hope we made the context much easier to study.
God bless you, Future doctors.

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