Pharmacology
Team 437

Drugs used in male infertility

Objectives:

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

Revised By
Hadeel Awartani
Abdullah AlOmar

Color index:
Important Note Extra

MED437
KING SAUD UNIVERSITY

Introduction

Infertility

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

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

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)**

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

1. **Idiopathic** (causes unknown). (Most common)
2. **Pre- testicular causes (poor hormonal support & poor general health) including:** Hypogonadism, Drugs, alcohol, Tobacco, Strenuous riding (bicycle & horse riding (Constant compression on testes) & sauna) causes ↑ temperature on the testes, Medications (chemotherapy, anabolic steroids the mechanism is the exogenous androgens will be converted into estrogen causing suppression of testosterone secretion → gynecomastia and small testes).
3. **Testicular causes (testes produce semen of low quantity and/or poor quality):** Age, Malaria, Testicular cancer, Idiopathic (unexplained sperm deficiencies).
4. **Post- testicular causes (conditions that affect male genital system after sperm production):** Vas deferens obstruction, Infection (e.g. prostatitis, T.B), Ejaculatory duct obstruction, Impotence. Affect delivery of sperms

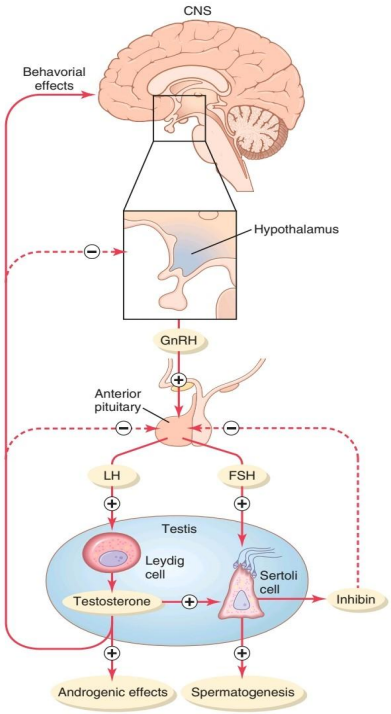
Pathophysiology

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- Convert T in seminiferous tubule to **(DHT)** and **Estradiol** → (+ve feedback on leydig C and –ve feedback estrogen has more potent negative feedback than testosterone on ant. Pit. hypothalamus)

4- LH: will act on leydig cell lead to secrete testosterone → (negative feedback on anterior pituitary and hypothalamus)



Male infertility:

1. Pre-testicular: Problems related to Hormone Production
2. Testicular: Problems related to Sperm Production
3. Post-testicular: Problems of Sperm Transport or Problem in Erection & Ejaculation

Treatment

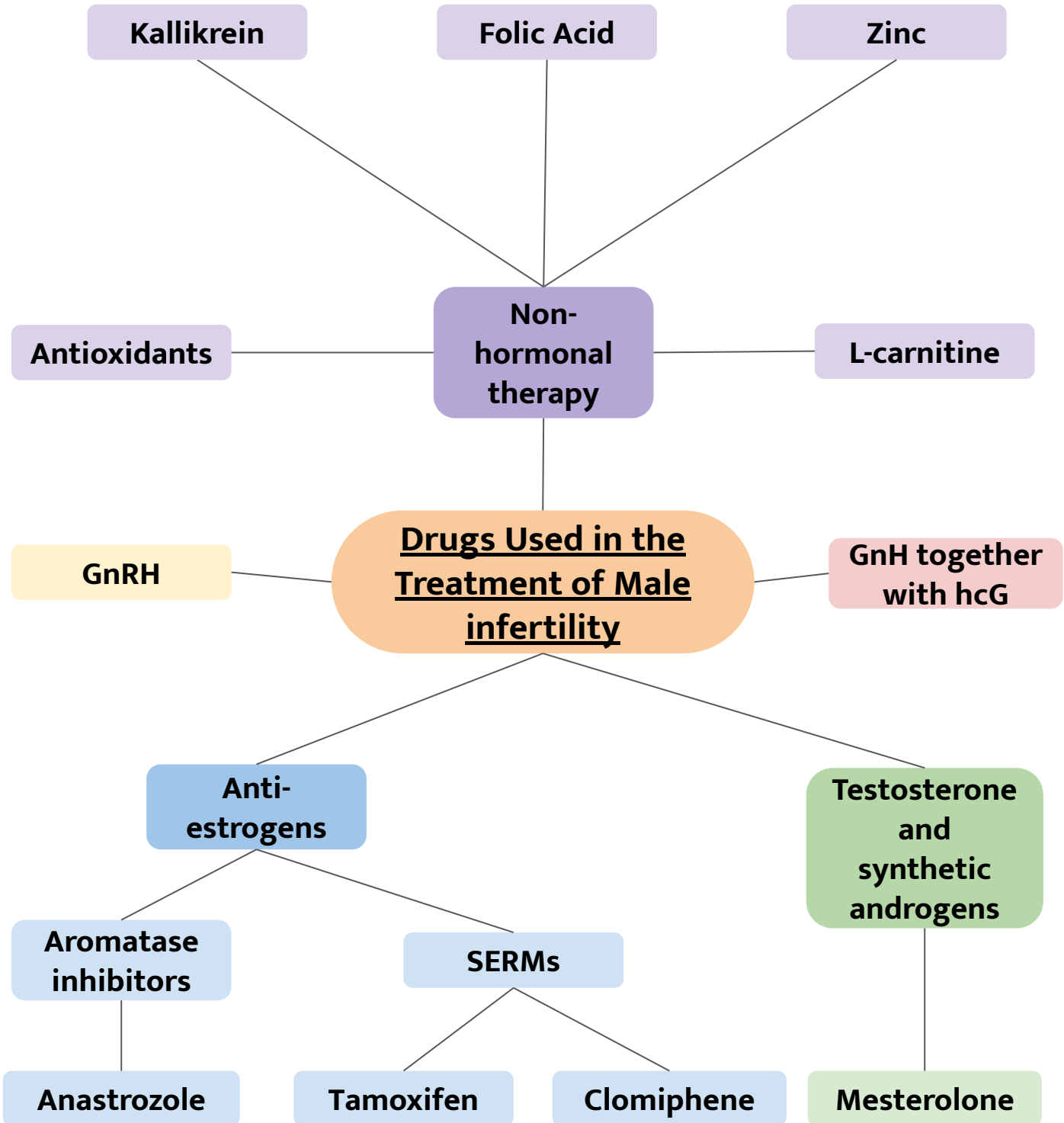
LH → Testosterone → Pulsatile (chronic LH → makes testis refractory)

Drug Treatment Of Male Infertility (Needs 3 months before semen quality changes)

Hormonal therapy	Specific (Clear reason)	Hyperprolactinaemia (Causes low LH & testosterone)	DA_2. Agonists
		Hypothyroidism	Thyroxine Can cause hyperprolactinemia
		Congenital adrenal hyperplas 21 α hydroxylase deficiency	Glucocorticoids excess Especially in people who're taking prednisone or prednisolone in asthma and RA, so they'll have high levels of cortisol which suppresses LH
	Emperical (Unknown reason)	Idiopathic	Androgens, Antiestrogen, GnH (FSH)
		Euogonadotrophic hypogonadism (↓T only) Functioning pituitary and non-functioning gonads but low testosterone	Antiestrogens (SERMs & Aromatase Is)
		Hypogonadotrophic hypogonadism 2ndry Hypogonadism 'Hypothalamo-Pituitary' (↓T & ↓ FSH / LH) The problem in hypothalamus or pituitary	Pulsatile GnRH, hCG, hMG, Androgens, Clomiphene (When the problem in pituitary gland)
Non-hormonal therapy Usually not infertility but impotence	Specific	Erectile dysfunction	PDE 5 inhibitors, e.g. sildenafil (viagra), vardenafil (levitra), tadalafil (cialis)
		Premature ejaculation	SSRIs (e.g. prozac)
		Infection of testes, prostate & UT	Antibiotics
	Emperical		Kallikrein, Antioxidants; e.g. vit E, vit.c, Zinc Supplements, Folic acid, L-Carnitine اغلب الحالات مايكون معروف سبب العقم

Hypergonadotrophic Hypogonadism (Testicular dysfunction) → 1ry Hypogonadism (↓T & ↑LH) Assisted Reproduction (no treatment) we have enough hormones but no functioning testes

Mindmap


Kallikrein
Folic Acid
Zinc
Non-hormonal therapy
Antioxidants
L-carnitine
Drugs Used in the Treatment of Male infertility
GnRH
GnH together with hcG
Anti-estrogens
Testosterone and synthetic androgens
Aromatase inhibitors
SERMs
Anastrozole
Tamoxifen
Clomiphene
Mesterolone

Testosterone

Testosterone and synthetic androgens

General 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.

P.K

Natural androgens:

- Ineffective orally (inactivated by first pass metabolism). I.M or S.C.
- skin patch & gels are also available.
- Binds to sex hormone binding globulin [SHBG].
- T1/2= 10-20 min.
- Inactivated by liver.
- 90% of metabolites → excreted in urine.
- **Disadvantages**: Rapidly absorbed, rapidly metabolized(short duration of action).

Synthetic Androgens (better):

- Less rapidly metabolized & more lipid soluble → increasing its duration of action.
- Derived from Testosterone.
- Esters: **propionate**, **enanthate**, **cypionate**→ in oil for IM (every 2-3 weeks).
- Other derivatives as: **Fluoxymesterone**, **Methyltestosterone**, **Danazol**→ given orally (daily).
- Derived from DHT as Mesterolone: given orally (daily). The most important one → because it will not be converted into estradiol so we won't have the effects of negative feedback.

M.O.A

I. Prostate, seminal vesicles convert testosterone by 5α-reductase to 5DHT → go to the cytoplasm of the target tissue→ bind to DNA (androgen receptor element), → transcribed into mRNA → translated → androgenic effects.

II. Testosterone 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.

III. **Brain**: estradiol serves as the most important feedback signal to the hypothalamus (esp. affecting LH secretion) which lead to suppression of testosterone secretion.

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).

Cont'd.

Pharmacological actions	1- Virilizing Effects: • Gonadotropin regulation. • Spermatogenesis. • Sexual dysfunction (this happen if it exceed the normal range) • Sexual restoration and development. 2- Protein anabolic effects: (anabolic steroids, not used in infertility) • Increase bone density. • Increase muscle mass. • Increase red blood cell mass.
C.I	➔ Male patients with cancer of breast or prostate. ➔ Severe renal & cardiac disease predispose to edema. ➔ Psychiatric disorders. ➔ Hypercoagulable states. ➔ Polycythemia
Interactions	★ Corticosteroids, they both cause edema. ★ Warfarin: Testosterone ↓ Warfarin metabolism → ↑bleeding. ★ Insulin or oral hypoglycemics + Testosterone cause hypoglycemia. ★ Propranolol: Testosterone↑ Propranolol Clearance → ↓Propranolol Efficacy. ★ Previous Effects of testosterone are because it effects on the renal tubules not the liver.
ADR	❖ Excess androgens (if taken > 6 wks) can cause impotence, decreased spermatogenesis & gynecomastia. ❖ Alteration in serum lipid profile: ↓HDL & ↑LDL, hence,↑risk of premature coronary heart disease. ❖ Salt & water retention leading to edema. ❖ Hepatic dysfunction:↑AST levels,↑alkaline phosphatase, ↑bilirubin & cholestatic jaundice. ❖ Hepatic carcinoma (long term use). ❖ Behavioral changes: physiologic dependence, aggressiveness, psychotic symptoms. ❖ Polycythemia (increase number of RBC) → ↑risk of clotting ❖ Premature closing of epiphysis of the long bones. ❖ Reduction of testicular size.
Important notes	**Mesterolone: More safely given in decrease testosterone or in 2ndry hypogonadism. Why?** (Does not cause premature closure of epiphyseal plates) 1. Not aromatized into estrogens → no –ve of GnHs→ encourages natural Testosterone production → spermatogenesis is enhanced. (No negative feedback) 2. Unlike other oral synthetic androgens it is not hepatotoxic.

Anti estrogens

	SERMs e.g. **Tamoxifen, Clomiphene**	Aromatase inhibitors e.g. **Anastrozole**
M.O.A	• Because estrogens → negative feedback on hypothalamus → decrease GnRH pulse frequency & pituitary responsiveness to GnRH, so antiestrogens → increase GnRH (FSH +LH) & improve its pituitary response. • **Only in Aromatase Inhibitors:** Blocks conversion of testosterone to estrogen within the hypothalamus.	
P.K	———————	Given as daily dose over a period of 1–6 months.
Indications	• All are used for inducing spermatogenesis in oligospermia (count is low). • Best to improve sperm count & motility with good pregnancy rates	
ADR	• Both drugs (**Tamoxifen, Clomiphene**) can induce libido & bad temper in men	———————

Other drugs

	GnRH	GnHS
M.O.A	Exogenous excess of GnRH → down-regulation of pituitary GnRH receptors & decrease LH responsiveness.	Increase spermatogenesis
P.K	Given as Pulsatile GnRH therapy (4-8 ug subcut every 2 hours) using a portable pump.	GnHS replacement must combined hCG^2 (IM for 2 Ms.) followed by hCG + hMG^2 (IM for 6-12 Ms.) (Because HCG has LH so restores deficiency)
Indications	Used in hypothalamic dysfunction bc they will cause androgenization & spermatogenesis.	Used in 2ndry hypogonadism i.e. problem in pituitary (FSH or both FSH or LH absent), bc it cause spermatogenesis.
ADR's	Headache, depression, generalized weakness, pain , gynecomastia and osteoporosis	Headache, local swelling (injection site), nasua, flushing, depression, gynecomastia, precocious puberty

Non-Hormonal Therapy

- Used in mild cases of infertility
- Hormone therapy is used if there is hypogonadism

Antioxidants	Protect sperm from oxidative damage (e.g. vit E, C) because ROS damages the membrane of the sperms.
Kallikrein	• Has proteolytic activity, cleaving kininogen to kinins which is important for sperm motility. • It enhances the sperm motility, so the doctor prescribe it if there is any abnormality in the sperm motility
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	Is important for sperm maturation. Taken as tablets

Summary

Testosterone and synthetic androgens

M.O.A	1. Prostate and seminal vesicles: converted to DHT by by 5-alpha reductase giving androgenic effect. 2. Bones: metabolized to estradiol by C-P450 aromatase which accelerate maturation of cartilage to bones. 3. Brain: converted to estradiol by C-P450 aromatase giving an important negative feedback signals to the hypothalamus.
Actions	A. Virilizing effects: • Gonadotropin regulation. • Spermatogenesis. • Sexual restoration and development. B. Protein anabolic effects: • Increase bone density. • Increase muscle mass. • Increase RBCs mass.
Uses	In androgen deficiency in adult male infertility and delayed puberty in hypogonadism.
C.I	• Male with breast or prostate cancers. • Severe renal and cardiac diseases. • Psychiatric disorders. • Hypercoagulable state and Polycythemia.
Interaction	• Corticosteroids, both causes edema. • Warfarin → Bleeding. • Insulin and oral hypoglycemic. • Propranolol → ↓efficacy.
Important	Mesterolone: More safely given in decrease testosterone or in 2ndry hypogonadism. Why? 1. Not aromatized into estrogens → no –ve of GnHs → encourages natural testosterone production → spermatogenesis is enhanced 2. Unlike other oral synthetic androgens it is not hepatotoxic.

Summary

	uses
GnRH	• Used in hypothalamic dysfunction and causes androgenization and spermatogenesis. • Given as pulsatile GnRH therapy using portable pump. • Excessive exogenous GnRH causes down regulation of Pituitary GnRH receptors and decreases LH receptors.
GnHs	Used In secondary hypogonadism to increase spermatogenesis.

	SERMs E.g. Tamoxifen, Clomiphene	Aromatase Inhibitors e.g.Anastrozole
MOA		Blocks conversion of testosterone to estrogen within the hypothalamus.
	Because estrogens → negative feedback on hypothalamus→ decrease GnRH pulse frequency & pituitary responsiveness to GnRH , so antiestrogens → increase GnRH & improve its pituitary response.	
Uses	• All are used for inducing spermatogenesis in oligozoospermia (count is low). • Best to improve sperm count & motility with good pregnancy rates.	

Non-hormonal Therapy	
Antioxidants	Protect sperms from oxidative damage (e.g. vit E,C).
Kallikrein	Has proteolytic activity, cleaving kininogen to kinins which is important for sperm motility.
Folic acid	Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties.
Zinc	Plays an important role in testicular development, sperm motility, and sperm production.
L-carnitine	Important for sperm maturation.

Quiz

Q1: Which of the following is Derived from Dihydrotestosterone ?
A.Cypionate.
B.Fluoxymesterone.
C.Mesterolone.
D.Danazol.

Q2: Which of the following BEST describes the mechanism of action of Anastrozole?
A. Mimic the natural action of testosterone.
B. Antagonize the action of estrogen on its receptors in hypothalamus.
C. Inhibit Aromatase enzyme and prevent the conversion of testosterone into estradiol.
D. Increase spermatogenesis by preventing the negative feedback to pituitary gland .

Q3: A drug that induce bad temper?
A- cypionate.
B- Tamoxifen.
C- Anastrozole.
D- Danazol.

Q4- which of the following is common ADRs of methyl-testosterone especially in children & teenagers?
A- osteoporosis.
B- Anemia.
C- Muscle atrophy.
D- Short stature & premature fusion of epiphyses.

Q5- Which of the following enhances spermatogenesis by encouraging the natural testosterone production?
A- Fluoxymesterone.
B- Mesterolone.
C- Danazol.
D- Cypionate.

Q6- which of the following drugs cause precocious puberty as a side effect ?
A-GnHS
B-GnRH
C-Danazol
D-Cypionate

Q7-A 35 male with infertility due to abnormal sperm motility, which of the following non-hormonal therapy should he use?
A-Antioxidant
B-L-carnitine
C-Kallikrein
D-Folic acid

Q8-A 33 years old patient on GnRH, which of the following side effect could he come with ?
A-Osteoporosis
B-Flushing
C-Hepatic carcinoma
D-Polycythemia

Answers:
1- C 6-A
2- C 7-C
3- B 8-A
4- D
5- B

Team Leader:

Abdullah Alsergani **Alanoud Salman**

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Notes by

Hmood alzaid

References:

- Team 436
- Doctors' slides and notes

@Pharma4370 Pharm437@gmail.com