Lecture 9

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 emperical non-hormonal therapies

- Additional Notes
- Important
- Explanation –Extra-

before starting, please check our Reproductive block correction

For any correction, suggestion or any useful information
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MALE 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

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 (oligospermia)**
- **Sperms are absent in the ejaculate (azoospermia)**
- **Sperm motility is seriously affected (asthenospermia)**
- **Sperms are totally immobile or dead (necrospermia)**

Physiology of spermatogenesis

you already know it but refresh your memory

Pulsatile Secretion of **GnRH** from hypothalamus will stimulate anterior pituitary to secrete **gonadotropin** (**FSH**,**LH**) that will lead → Initiation & Maintenance of spermatogenesis:

1-LH: will act on leydig cell lead to secrete **testosterone**→(-ve on anterior pituitary, hypothalamus)

2-FSH: will act on sertoli cell in seminiferous tubule lead to release **inhibin**→(-ve on anterior pituitary), and convert testosterone in seminiferous tubule to **dihydrotestosterone** [DHT] and **Estradiol**→(+ve on leydig cells and -ve on anterior pituitary, hypothalamus)

note: LH→Testosterone in a Pulsatile manner

(chronic LH → makes testis refractory)

MALE INFERTILITY

PRE-TESTICULAR	TESTICULAR	POST-TESTICULAR
1. Problems related to Hormone Production	2. Problems related to Sperm Production	3. Problems of Sperm Transport 4. Problem in Erection & Ejaculation
Causes:		
(poor hormonal support & poor general health) including: • **Hypogonadism** • **Drugs** • **Alcohol** • **Tobacco** • **Strenuous riding (bicycle & horse riding)** • **Medications (chemotherapy; anabolic steroids).**	**(testes produce semen of low quantity and/or poor quality):** • **Age** • **Malaria** • **Testicular cancer;** • **Idiopathic (unexplained sperm deficiencies).**	**(conditions that affect male genital system after sperm production):** • **Vas deferens obstruction;** • **Infection e.g. prostatitis, T.B** • **Ejaculatory duct obstruction** • **Impotence.**

★ **it could be none of above causes → Idiopathic**

DRUG TREATMENT OF MALE INFERTILITY

(Needs 3 months before semen quality changes)

HORMONAL THERAPY

SPECIFIC	• **Hyperprolactinaemia** ➡ ***DA_2 Agonists*** • **Hypothyroidism** ➡ ***Thyroxine*** • **Congenital Adrenal Hyperplasia** ➡ ***Glucocorticoids excess***
EMPERICAL (not specific)	• **Idiopathic** ➡ ***Androgens, Antiestrogen, GnH(FSH)*** • **Euogonadotrophic Hypogonadism** ***(⬇T only)*** ➡ ***Antiestrogens (SERMs & Aromatase Is inhibitors)*** • **Hypogonadotrophic hypogonadism** ➡ **2ndry** ***Hypogonadism (Hypothalamo-Pituitary) ⬇T & ⬇ FSH / LH → Pulsatile GnRH, hCG, hMG, Androgens, Clomiphene*** • **Hypergonadotrophic Hypogonadism** (Testicular dysfunction) ➡ 1ry Hypogonadism (⬇T & ⬆ LH) ***Assisted Reproduction (no treatment)***

NON-HORMONAL THERAPY

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***

1-Testosterone

Principle male sex hormone produced in testis(> 95%), small amount in adrenals. It follows a circadian pattern leads to ⇧ in **early morning** & ⇩ in **evening**.

MOA of Testosterone

- ❖ Testosterone is converted in **accessory sex organs** (prostate and seminal vesicles) by **5 a reductase** to DHT → Proteins → **Androgenic effect**
- ❖ Testosterone is converted in **bones, brain, adipose tissue and liver** by **aromatase** enzyme to estrogen

In bones and brain :

Testesterone 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 effect of Testosterone

Virilizing effect:

- ❑ **Gonadotropin regulation**
- ❑ **Spermatogenesis**
- ❑ **Sexual dysfunction**
- ❑ **Sexual restoration and development**

Protein anabolic effect:

- ❑ **increase bone density**
- ❑ **increase muscle mass**
- ❑ **increase red blood cell mass**

Note:

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

1-Testosterone

PharmacoKinetics of Testosterone	• **Ineffective orally** (inactivated by 1st pass met.) so we use **I.M or S.C.,** *Skin patch & gels are also available* • Binds to Sex Hormone Binding Globulin [**SHBG**] • **t1/2** = 10 –20 min **(short t1/2)** • **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**

Drugs	**1-Derived from Testosterone:** **a-Esters; propionate, enanthate, cypionate that ⇨ in oil for IM; every 2-3 weeks** **b-Other derivatives; as Fluoxymesterone, Methyltestosterone, Danazol ⇨ given Orally; daily** **2-Derived from DHT:** **Mesterolone ⇨ given Orally; daily**

1-Testosterone

Adverse effects

- **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) leads to ⇧risk of clotting.
- Premature closing of epiphysis of the long bones.
- Reduction of testicular size

Indication (Androgens)

As Testosterone Replacement therapy(TRT):

1-Therapy for androgen deficiency in adult male infertility.

2-In delayed puberty with hypogonadism ⟹ give androgen slow & spaced for fear of premature fusion of epiphyses ⟹ short stature.

Contraindication

1-Male patients with cancer of breast or prostate
2-Severe renal & cardiac disease ⟹ predispose to edema
3-Psychiatric disorders
4-Hypercoagulable states 5-Polycythemia

Mestrolone : More safely given in decreased testosterone or in 2ndry hypogonadism because :-

1. **Not aromatised** into estrogens → no –ve of GnHs → encourages natural testosterone production → **spermatogenesis is enhanced**
2. Unlike other oral synthetic androgens it is **not hepatotoxic**

Interactions

- with corticosteroids ⟹ oedema
- with warfarin leads to ⇩ metabolism ⟹ bleeding
- with insulin or oral hypoglycemics ⟹ hypoglycemia
- with propranolol leads to ⇧ propranolol clearance leads to ⇩ efficacy

2-Anti- Estrogens

Because estrogens –ve feedback on hypothalamus → ⇩**GnRH pulse frequency** & **pituitary responsiveness** to GnRH , so **antiestrogens** →⇧GnRH & improve its pituitary response.

SERMs: Tamoxifen,Clomiphene	Aromatase Inhibitors:Anastrozole
❖ Induce libido & bad temper in men	❖ Blocks **conversion** of testosterone to estrogen within the hypothalamus. ❖ Induce spermatogenesis in **oligozoospermia**(low count) ❖ Givens as a daily dose over a period of **1-6 mounth** ❖ **best to improve sperm count and motility with good pregnancy rates**

3-GnRH

- ❖ Used in **hypothalamic dysfunction→androgenization & spermatogenesis**
- ❖ 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 , gynecomastia and osteoporosis.**

4-GnHs

- ❖ Used in **2ndry hypogonadism** (FSH or both FSH or LH **absent**) →spermatogenesis
- ❖ GnHs replacement must be **combined**; **hCG** (3 x 2000 U/w. IM.**2 ms.**) followed by **hCG + hMG** (3x 75 to 3 x 150 U /w. IM. **6 -12 ms**).
- ❖ **ADRs; Headache, local swelling (injection site), nausea, flushing, depression, gynecomastia, precocious puberty.**

NON-HORMONAL THERAPY

(improve sperm quality and quantity.)

Antioxidants	Protects sperm from oxidative damage **(e.g. vit E & C)**
Kallikrein	Has a proteolytic activity, Cleaves **kininogen to kinin**→ (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 production & sperm motility.
L-Carnitine	Important for sperm maturation

MCQs

1-27 years old man married 2 year ago visit clinic due to inability to conceive doctor order hormonal profile for patient. result from lab shows decreased(testosterone,FSH ,LH) the doctor prescribed him which of the following?
A- Antiestrogens
B-Pulsatile GnRH
C-Thyroxine
D-Mesterolone

2- What is the pre-testicular cause of of male infertility?
A- Malaria
B- Vas deferens obstruction
C- Hypogonadism
D- Age

3- Azoospermia means:
A- count low
B- sperms are absent in the ejaculate
C- sperm motility is seriously affected
D- sperms are totally immobile or dead

4- Testosterone is converted to estrogen in adipose tissue by :
A-aromatase enzyme
B- 5- alpha reductase enzyme
C- lipase
D- no right answers

5- The patient who take the Testosterone with corticosteroids may develop :
A- Bleeding
B-Hypoglycemia
C- edema
D-Polycythemia

6- Which of the the following is one of the adverse effects of testosterone ?
A- dyslipidemia
B- Polycythemia
C- SLE
D- A and B

1-B
2-C
3-B
4- A
5- C
6- D

Done by Pharmacology team 434

Can you believe it ?!! We are almost (basic science years) free !!
A special thanks to our wonderful future doctors for their advices and their help in making Pharmacology teamwork:

- Abdullah Althuniyan
- Abdulrahman Almotairi
- Abdulrahman Alkaff
- Abdullah Alammari
- Hussain Alkaff
- Abdullah Alhmoodi
- Omar Rahbeeni
- Saad Altwairiqi
- Mashhoor Alzareie
- Moath Walbi
- Moath Aleisa
- Meshary Alsalem
- Nouf Aloraini
- Jumana Fatani
- Malak Alkhathlan
- Nada Alamri
- Asmaa Alrusaies
- Elham Alghamdi
- Futoon Almutairi
- Sarah M. Aljasser
- Rana Albarrak
- Mona Alqahtani
- Nouf Almasoud
- Lina Aljurf
- Ibtihal Almshawi
- Sarah Julaidan
- Noura Alhilali
- Nouf Alharbi
- Lulua Aldaej

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