Drugs in the treatment of male infertility

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introduction

- Definition of male infertility : **Inability of a male to achieve conception in a fertile woman after one year of unprotected intercourse**
- Prevalence : **Approximately 15-20% of all cohabiting couples are infertile In up to 50% of such cases, males are responsible**
- **What is impotence?**

Impotence is the failure of completion of sexual intercourse (no libido , difficulty in erection , etc..)

- **Some terminology of findings in the semen analysis of infertile male :**

1. **Count is low (oligospermia)**
2. **Sperms are absent in the ejaculate (azoospermia)**
3. **Sperm motility is seriously affected (asthenospermia).**
4. **Sperms are totally immobile or dead (necrospermia)**

- **Infertility in males could be due to**

✓ **Problems related to hormone production , referred to as : Pre-testicular**
✓ **Problems related to sperm production , referred to as : testicular**
✓ **Problems of sperm transport , referred to as : post-testicular**
✓ **Problems of sperm ejection and ejaculation also referred to as : post testicular**

Classification of treatment: (V.IMP)

u should memorize the Empirical (RED) only

1. Hormonal therapy:

a. Specific (treating the cause):

i. Infertility due to hyperprolactenimea→ use dopamine receptor(DA2) agonists

ii. Infertility due to hypothyroidism → use thyroxin

iii. Infertility secondary to CAH (congenital adrenal hyperplasia) →use glucocorticoids

b. Empirical (treating without knowing a specific cause):

i. Euogonadotrophic Hypogonadism (euogonadotrophic: normal hormones , LH & FSH):

1. **↓Decrease in testosterone only**
2. **Treatment: anti-estrogens**
   a. **SERMs**
   b. **Aromatase inhibitors**

ii. Idiopathic hypogonadism

1. **Treatment:**
   a. **Androgens**
   b. **Anti estrogens**
   c. **FSH**

iii. Hypogonadotrophic hypogonadism :

1. **Also known as secondary hypogonadism, which means hypogonadism due to less gonadotrophins (LH and FSH) due to pituitary or hypothalamus related problems**
2. **↓Decrease in testosterone , ↓LH and ↓FSH**
3. **Treatment:**
   a. **Pulsatile GnRH**
   b. **hCG (FSH)**
   c. **hMG(LH)**
   d. **Androgens**
   e. **Clomiphene (SERM)**

iv. Hypergonadotrophic Hypogonadism

1. **Also known as primary hypogonadism**
2. **↓Decrease in testosterone , ↑increase in LH**
3. **Treatment : Assisted reproduction**

2. Non hormonal therapy :

a. Specific

i. Erectile dysfunction: treat with PDE-5 inhibitors

1. sildenafil(viagra) 2. vardenafil(levitra)
   3. tadalafil(cialis) 4. Alprostadil

ii. Premature ejaculation : treat with SSRI (selective serotonin reuptake inhibitors

iii. Infection of the testis and urinary tract and prostate : treat with antibiotics

b. Empirical we use multivitamins and supplements:

i. ***Kallikrein***
ii. ***Antioxidants; e.g.vit E, vit.c***
iii. ***Zinc Supplements***
iv. ***Folic acid***
v. ***L-Carnitine***

DRUG TREATMENT OF MALE INFERTILITY

HORMONAL THERAPY

EMPERICAL

- **Euogonadotrophic Hypogonadism →**
  (↓T only) Antiestrogen: SERMs & Aromatase Is
- **Idiopathic →** *Androgens, Antiestrogen, GnH(FSH)*
- **Hypogonadotrophic hypogonadism →** 2ndry *Hypogonadism (Hypothalamo-Pituitary)*
  (↓T & ↓FSH / LH)
  Pulsatile GnRH, hCG, hMG, Androgens, Clomiphene

NON-HORMONAL THERAPY

EMPERICAL

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

- **Hypergonadotrophic Hypogonadism →**
  Pry Hypogonadism (↓T &↑LH) *Assisted Reproduction*

First: androgens :

- **Principle male sex hormone** produced in testis from lyedig cells (> 95%), small amount in adrenals. It follows a circadian pattern ↑in early morning & ↓in evening
- **How does testosterone work?**

1. By binding and activation of androgen receptors **directly or as DHT**

   (Changed to dihydrotestosterone (DHT) in the accessory sex organs by the enzyme 5α-reductase)

2. Aromatization to estradiol By aromatase enzyme then binding to estrogen receptors
   a. Bones : accelerates maturation of cartilage into bone leading to closure of the epiphyses & conclusion of growth
   b. Brain : serves as the most important feedback signal to the hypothalamus(esp. affecting LH secretion)
   c. liver and adipose tissue

- **Actions of testosterone:**

1. Virilizing effects
   a. Gonadotropin regulation
   b. Spermatogenesis
   c. Sexual dysfunction
   d. Sexual restoration and development
2. Protein anabolic effects (can also be achieved by the use of anabolic steroids)
   a. Increased bone density
   b. Increase muscle mass
   c. Increased red blood cells

- **For pharmacological uses It can be found as :**
  - Testosterone
  - Synthetic androgens
    - Derived from Testosterone
      - Esters; proprionate, enanthate, cypionate
      - Or derivatives as Fluoxymesterone, Methyltestosterone, Danazol
    - Derived from DHT
      - Mesterolone (is not hepatotoxic)

- **Kinetics**
  - Binds to Sex Hormone Binding Globulin [SHBG]
  - t1/2 = 10 –20 min (**short**)
  - Inactivated in the liver. 90% of metabolites ➔excreted in urine.
  - Synthetic androgens ➔ **less rapidly metabolized** & some are excreted unchanged in urine

- **Method of administration**

1. **Testosterone** :
   a. Ineffective orally due to inactivation by first pass metabolism
   b. Given : I.M or S.C
   c. Also skin patches and gels

2. **Synthetic androgens**
   a. Derived from Testosterone
   i. Esters; proprionate, enanthate, cypionate
      - I.M every 2-3 weeks
   ii. Or derivatives as Fluoxymesterone, Methyltestosterone, Danazol
      - Orally , daily
   b. Derived from DHT
   i. Mesterolone (is not hepatotoxic)
      - Orally , daily

- **Indications:**

Testosterone replacement therapy is indicated in :

1. **Therapy for androgen deficiency in adult male infertility.**
2. **Patients with delayed puberty with hypogonadism**
   a. These patients are given testosterone slowly and spaced . Why ? because testosterone increases bone density and closure of the epiphysis of the bone which will lead to short stature if given fast.

- **ADR's**: are very simple if you know the physiological function

1. **Behavioral changes**
   a. physiologic dependence
   b. ↑ aggressiveness
   c. psychotic symptoms
2. **Azoospermia(sperms are absent in the ejaculate) & 2^{ndry} Gn H suppression (if taken > 6wks).**
   a. This happens because of chronic use of testosterone without proper admission , the constant release will suppress the release of LH/FSH permanently
3. **Alteration in serum lipid profile: ↓HDL & ↑LDL**
4. **Salt & water retention**
   a. This leads to increase weight (weight gain)
5. **Hepatic dysfunction;**
   a. ↑ AST levels,↑alkaline phosphatase,
   b. ↑ bilirubin & cholestatic jaundice.
6. **Masculinization**
7. **Acne**
8. **Polycythemia**(increase number of RBC)

- **Contraindications**

- Male patients with cancer of breast or prostate (androgens are a mediator of prostatic cancer)
- Severe renal & cardiac disease → predispose to edema
  - Because testosterone has sodium and water retention effects it could increase the load on the heart and alter the rennin angiotensin system in the kidney
- Psychiatric disorders
- Hypercoagulable states
- Polycythemia
- Pregnant women

- **Interactions**
  - Androgens + corticosteroids → leads to oedema (effect of testosterone and cortisol)
  - Androgens + warfarin →bleeding (androgen will decrease the metabolism of warfarin)
  - Androgens + insulin or oral hypoglycemic → hypoglycemia
  - Androgens + propranolol → decreased efficacy of propranolol (because androgens will increase the clearance of propranolol)

- **Mesterolone**:

Derived from DHT is a synthetic androgen. Used for the treatment of secondary hypogonadism and decreased levels of testosterone **more safely**. **Why?**

- **Not hepatotoxic**
- **Not aromatized into estrogens ((SO no** binding to estrogen receptors**))**
  This lead to >> **no –ve of GnHs ➔ encourages natural testosterone production & ↓ its binding to SHBG ➔ spermatogenesis is enhanced**

Second: GnRH

- **Used in hypothalamic dysfunction**
- **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
  - When used for long periods it causes desensitization of the receptors
- **ADR's**
  - Headache, depression, generalized weakness, pain & gynecomastia osteoporosis,

    neurological symptoms

Third: gonadotropins (LH & FSH)

- **Used in secondary hypogonadism** to increase 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, anaphylactic shock

Fourth: anti-estrogens:

Why do we use anti estrogens in the treatment of men infertility?

Answer: estrogens cause negative feedback on the hypothalamus that will cause a decrease in release of GnRH pulse & decrease the responsiveness of pituitary to GnRH

So when using anti-estrogens that will cause an increase in GnRH pulse frequency and improve the response of pituitary to GnRH. because the negative feedback of estrogens is blocked by anti-estrogens.

Because estrogens → –ve feedback on hypothalamus →↓ GnRH pulse frequency & pituitary responsiveness to GnRH , so antiestrogens →↑ Gn RH & improve its pituitary response.

1. **SERM's**
    a. **Tamoxifen**
    b. **Clomiphene**
2. **Aromatase inhibitors**
    a. **E.g : Anastrozole**
    b. They block the conversion of testosterone to estrogen in the hypothalamus

- **Used** in : inducing spermatogenesis **in oligozoospermia** (low sperm count)
- **Given** daily for a period of 1-6 months
- Best to **improve sperm count & motility** with good pregnancy rates

Fifth : non hormonal therapy:

Sometimes very promising in improving sperm quality and quantity

1. **Antioxidants**: protect sperm from oxidative damage
2. **Kallikrien** : Has **proteolytic activity**, cleaving kininogen to kinins→ important for **sperm motility (improve (asthenospermia).**
3. **Folic acid** : Plays a role in RNA and DNA synthesis during spermatogenesis & has antioxidant properties
4. **Zinc** : Plays an important role in **testicular development, spermatogenesis & sperm motility**
5. **L-CARNITINE** : Is highly **concentrated in the epididymis** & are important **for sperm metabolism & maturation**

!! Mesterolone & Aromatase inhibitors Have less chance of feminization than