Drugs used in Male Infertility

	MOA	Pharmakokinetics	Administration
1) **Androgens:** • Testosterone (Natural) • Synthetic: - Esters: proprionate, enanthate, cypionate. - Testosterone Derivatives: Fluoxymesterone, Methyltestosterone, Danazol - **Derived from DHT;** Mesterolone	A) **It or its DHT metabolite bind to Androgen Receptors [AR]:** 1. **Cytosolic** ➔GENOMIC Action ➔mediates cell growth & differentation in AR responsive tissues: reproductive, those of 2ndry male sex characters, muscles 2. **Membranous** ➔ NON-GENOMIC Action ➔ mediates rapid responses ➔ on some brain, CVS, T cell functions B) **The aromatization of testosterone to estrogen and then binding to the estrogen receptor:** Estradiol rather than testosterone: Testesterone is metabolized to estradiol by Cytochrome -p450 aromatase, mediates actions in bones and some brain areas.	• Binds to **Sex Hormone Binding Globulin [SHBG]** • t1/2 = 10 –20 min • **Inactivated in the liver**; 90% of metabolites ➔excreted in urine. • Synthetic androgens ➔ less rapidly metabolized & some are excreted unchanged in urine	RegularTestosterone(inactivated by 1st pass met.)→ so it is given by I.M or S.C. Skin patch (genitial and non-genitial) & even gels are also available. - Esters: proprionate, enanthate, cypionate → in oil for IM; every 2-3 weeks. - Other derivatives as Fluoxymesterone, Methyltestosterone, Danazol → given Orally; daily - Derived from DHT; **Mesterolone** → given Orally; daily (doesn't have 1 rst pass met.)

Indications of Androgens	ADRs	Contraindications	Drug Interaction
A. **In Male infertility:** 1. Low dose oral (methyltestosterone 10-50 mg/day)or (fluoxymesterone 5-20 mg/day) may improve epididymal function & ↑ sperm motility . 2. High dose exogenous testosterone given then abruptly stopped. B. **As androgen replacement therapy:** In delayed puberty with hypogonadism → give androgen slow & spaced for fear of premature fusion of epiphyses → short stature	A. **In Females:** Masculinization & Virilization B. **In Males:** 1. Prostatic hyperplasia 2. 2ndry GnH(gonadotrophs) suppression; azoospermia (Sperms are absent in the ejaculate), impotence, gynecomastia (If taken >6 wks). 3. Short stature due to premature closure of epiphysis (before 18 years) C. **General Effects:** 1. CNS manifestations. 2. Alteration in serum lipid profile: ↓HDL & ↑LDL; ↑risk of ACS 3. Salt & water retention 4. Hepatic dysfunction;↑ AST levels,↑alkaline phosphatase, ↑ bilirubin & cholestatic jaundice. Most oral preparations are hepatotoxic → adenomas & carcinomas 5. Polycythemia→ increase risk of clotting	- Male patients with cancer of breast or prostate. - Severe renal & cardiac disease → predispose to edema. - Psychiatric disorders. - Hypercoagulable states. - Polycythemia -Pregnancy: possible virilization of the female fetus and undermusculinization of a male fetus.	1. All forms + corticosteroids → oedema 2. All forms + warfarin → ↓metabolism → ↑ bleeding 3. Synthetic Androgens + insulin or oral hypoglycemics → hypoglycemia 4. Testosterone +propranolol → ↑ propranolol clearance → ↓efficacy

Mesterolone: is an oral synthetic androgen derived from **DHT**.	It is more safely given if ↓testosterone or in 2ndry hypogonadism. 1. Not aromatised into estrogens/ no binding to estrogen receptors. 2. Unlike almost all other orals synthetic androgens it is not hepatotoxic; not -alkylated but methylated → less hepatic complications

	Uses	MOA/PKA	ADRs
2) **GnRH**	Used in hypothalamic dysfunction→androgenization & spermatogenesis	Given as Pulsatile GnRH therapy (4-8 ug subcut every 2 hours) using a portable pump. Less use by intranasal or intravenous routes. Exogenous excess of GnRH →down-regulation of pituitary GnRH receptors & ↓ LH responsiveness.	-Headache -Depression -Generalized weakness -Gynecomastia -Osteoporosis -Neurological symptoms
3) **GnH**	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). rhFSH alone → little efficacy	-Headache -Local swelling (injection site) -Nausea -Flushing -Depression -Gynecomastia -Precocious puberty -Anaphylactic shock.
4) **Anti-estrogens:** A] **SERMs** (Tamoxifen, Clomiphene)	* Tamoxifen→↑ GnRH, but has its own estrogen agonistic property → feminizing side effects. * Clomiphene→ has less estrogenic agonistic property. Yet both drugs can induce libido & bad temper in men.		
B] **Aromatase inhibitors** (Anastrazole)	* Blocks conversion of testosterone to estrogen within the hypothalamus * All are used for inducing spermatogenesis in oligozoospermia * Given as daily dose over a period of 1–6 months. * Best to improve sperm count & motility with good pregnancy rates		

Non-Hormonal Therapy

1) Antioxidants	Protect sperm from oxidative damage.
2) Kallikrein	Has proteolytic activity, cleaving kininogen to kinins →important for sperm motility.
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.

Summary

• **ANDROGENS** follow a circadian pattern➔↑in early morning & ↓in evening
• Androgens In prostate,seminal vesicles&skin converted by **α-reductase** to **DHT** and In Bones: premature closure of the epiphyses.
• ANDROGEN can be givin in delayed puberty with hypogonadism give androgen slow & spaced for fear of premature fusion of epiphyses.
• **Androgens can cause:**
  - Masculinization effects In Females, impotence,decreased spermatogenesis & gynecomastia in male.
  - Alteration in serum lipid profile: ↓HDL & ↑LDL
  - Edema → contraindicated in Severe renal & cardiac disease
  - Hepatic dysfunction.
  - Behavioral changes → it's contraindicated in Psychiatric disorders
  - Polycythemia ➔ it's contraindicated in Hypercoagulable states and Polycythemia
  - It's contraindicated in Male patients with cancer of breast or prostate
• **Androgens Interactions:**
  - All forms + corticosteroids ➔ oedema
  - All forms + warfarin ➔ ↓metabolism ➔ ↑ bleeding
  - Synthetic Androgens + insulin or oral hypoglycemics ➔ hypoglycemia
  - Testosterone + propranolol ➔ ↑ propranolol clearance ➔ ↓efficacy

• **Mesterolone** is Synthetic Androgens used in 2ndry hypogonadism, derived from DHT given **orally** (doesn't have 1rst pass met.)
  1. Not aromatised into estrogens (no feminization) + binds to estrogen receptors➔no –ve of GnHs ➔ spermatogenesis is enhanced.
  2. Not hepatotoxic.
• **GnHs** and **GRHs** are Used in hypothalamic dysfunction (secondary hypogonadisim) ➔androgenization & spermatogenesis
• **Clomiphene** Is Antiestrogens (**SERMs**) can induce libido & bad temper in men
• **Anastrozole** is Aromatase Inhibitors it Blocks conversion of testosterone to estrogen within the hypothalamus and has good pregnancy rates
• **NON-HORMONAL THERAPY** are also used as treatment of infertility as: **Kallikrein**, **Antioxidants** (e.g.**vit. E** and **vit.C**), **Zinc Supplements**, **Folic acid**, **L-Carnitine**